PAROXETINE MESYLATE 7.5 MG
ADVISORY COMMITTEE BRIEFING DOCUMENT

NDA #204-516

Reproductive Health Drugs Advisory Committee Meeting

March 4, 2013

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350 Fifth Avenue
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EXECUTIVE OVERVIEW

Introduction

Millions of women suffer from what can be debilitating menopausal vasomotor symptoms (VMS). Currently the only approved treatment option is hormone therapy (HT). Although often effective in this setting, HT is not appropriate for every patient and some women are unwilling or unable to take HT based on the current prescribing information or perceived risks, including breast and endometrial cancer and cardiovascular complications. Given the limitations of HT both in terms of physician use and patient acceptance, many physicians prescribe neuropsychiatric medications off-label to treat VMS. Most often, they use selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Noven Pharmaceuticals has developed paroxetine mesylate 7.5 mg referred to as Low Dose Mesylate Salt of Paroxetine (LDMP) specifically to treat moderate to severe VMS associated with menopause. LDMP is an SSRI, and its mechanism of action for VMS is thought to be related to the potentiation of neurotransmitters in the central nervous system that affect regulation of body temperature control (Bachmann 2005; Rossmanith and Ruebberdt 2009). LDMP has a paroxetine dose substantially lower than those currently prescribed for psychiatric indications (10 to 60 mg) and lower than the most commonly used off-label doses of paroxetine to treat VMS (20 mg and 40 mg). Unlike the higher psychiatric doses, LDMP does not require up or down titration.

The LDMP clinical development program included one Phase 2 trial, two pivotal Phase 3 trials, and one single- and multiple-dose pharmacokinetics (PK) trial. The Phase 2 trial demonstrated proof of concept and the Phase 3 trials demonstrated efficacy for the treatment of moderate to severe VMS that persisted over time (24 weeks). LDMP was well tolerated based on the assessment of 635 postmenopausal women who were randomized to receive LDMP in the clinical development program.

Medical Need

Menopause is a natural part of a woman's life, with associated symptoms that may range from mild and occasional to debilitating and frequent. VMS, which includes hot flashes and night sweats, is the most commonly reported symptom, occurring in up to 75% of postmenopausal women (Feldman et al 1985). Hot flashes are a spontaneous sensation of warmth associated with perspiration, anxiety, and palpitations (Nelson et al 2006), which may occur weekly or monthly or as frequently as daily or hourly.

The US Food and Drug Administration (FDA) defines mild, moderate, and severe VMS as follows (Guidance for Industry, January 2003):

- Mild: hot flashes without sweating
- Moderate: hot flashes with sweating and being able to continue an activity
- Severe: hot flashes with sweating and the inability to continue an activity

The majority of women experience symptoms for 6 months to 2 years (Utian 2005; Warren 2010). In many women, VMS is severe enough to interrupt their daily personal and professional activities and prevent a full night's sleep (Fugate and Church 2004; Nelson et al 2006; Pachman et al 2010; Rapkin 2007). VMS may also interfere with relationships at home or work (Woods et al 2011). Because VMS has multiple manifestations and wide-ranging effects on quality of life, there is no single, simple approach for assessing the effectiveness and clinical meaningfulness of treatment for VMS.

LDMP was developed for the treatment of moderate to severe VMS in postmenopausal women. The pivotal trials enrolled women who were experiencing at least 7 moderate to severe hot flashes per day or at least 50 per week. This frequency of moderate and severe hot flashes represents a substantial burden on patients. The studies included multiple questionnaires to assess the impact of VMS on their lives as well as the potential of LDMP to diminish this impact.

Currently the only FDA-approved treatment option for VMS is HT. Although often effective in this setting, HT is not appropriate for every patient. The prescribing information of HT lists contraindications for women with a history of breast or estrogen-dependent neoplasia; thus, many women are reluctant to take HT because of perceived risks.

Given the limited approved treatment options, many physicians prescribe neuropsychiatric medications off-label to treat VMS. Most often, they use SSRIs and SNRIs. Each year, women aged 40 to 65 years receive 4.5 million prescriptions of paroxetine for approved indications. In the past year, 3.3 million prescriptions were filled for SSRIs and SNRIs to treat VMS. Of these prescriptions, 2.4 million were for SSRIs and more than 250,000 were for paroxetine. The most common dosage strengths of paroxetine prescribed off-label for VMS were 20 mg (112,000 prescriptions) and 40 mg (52,700 prescriptions) (IMS NPA Market Dynamics™ for the period December 2011 to November 2012).

SSRIs and SNRIs are approved for psychiatric indications and lack an approved prescribing information label to guide appropriate use in VMS. Of particular concern to menopausal women is the potential for weight gain and sexual dysfunction, which are often associated with psychiatric doses of SSRIs and SNRIs.

Only 17% of women with moderate to severe hot flashes currently receive a prescription of either HT or an off-label medication (Williams et al 2007). Many women with VMS resort to unproven remedies and herbal supplements, which are unregulated and have been found to be

ineffective in most controlled studies (Nelson et al 2006). There is an unmet need for additional treatment options.

Development History

Noven sought to develop a nonhormonal treatment for moderate to severe VMS. The company began with a literature search for existing drugs with evidence of effectiveness in treating VMS.

Noven chose to develop a new product with a lower dose of paroxetine mesylate than those available for psychiatric indications (Stearns et al 2003a, Gordon et al 2006, Kimmick et al 2006, Grady et al 2007). Paroxetine had been found to be effective for the treatment of VMS at higher doses in several small pilot studies (Stearns et al 2003a) and is among the most effective SSRIs studied for this condition (Loprinzi et al 2009). The literature showed that across the dose range studied there was no dose relationship for efficacy, but there was a dose relationship for tolerability. Based on this review, Noven hypothesized that a product with a lower dose of paroxetine mesylate than those prescribed for psychiatric disorders could be effective for treating VMS while having lower incidence of side effects, such as weight gain, sexual dysfunction, and discontinuation symptoms, which are associated with higher doses.

Paroxetine mesylate was approved by the FDA in 2003 at doses ranging from 10 to 60 mg daily for the treatment of major depressive disorder, obsessive compulsive disorder, and panic disorder with or without agoraphobia, and in 2006 it was approved for generalized anxiety disorder. Noven markets a paroxetine mesylate product for psychiatric indications under the trade name PEXEVA®. Paroxetine hydrochloride, which is the same active ingredient formulated with a different salt, has been approved since 1992 for multiple psychiatric indications under the trade name Paxil.

Because of the well-established safety profile of paroxetine at higher doses, FDA agreed that Noven could develop the LDMP product under the 505(b)(2) pathway, relying on FDA's findings of safety for Paxil and referencing the nonclinical and clinical pharmacology data previously submitted in the Pexeva New Drug Application (NDA). The Pexeva NDA included studies directly comparing Paxil and Pexeva that demonstrated no difference in toxicity, mutagenicity, or PK parameters of the two salt forms; therefore, no new nonclinical or safety studies were required during the development of LDMP.

In 2008, Noven initiated a proof-of-concept Phase 2 study (N30-002) with LDMP for the treatment of moderate to severe VMS associated with menopause. The 7.5 mg dose was chosen because it is substantially lower than the doses of paroxetine most commonly used off-label to treat VMS (20 mg and 40 mg). Results of the Phase 2 study provided proof of concept and showed that the 7.5 mg dose was well tolerated. This study also informed the estimation of effect size for the Phase 3 development program, and the results reflected the high placebo response seen in the literature for VMS (Stearns et al 2000, Stearns et al 2003a, MacLennan et al 2004, Stearns 2005, Nedrow et al 2006).

The Phase 3 program comprised 2 pivotal trials (Study N30-003 and Study N30-004). Both protocols reflected FDA feedback, and Study N30-003 was conducted under a Special Protocol Assessment (SPA), whereby FDA reviewed the study design, clinical endpoints, and statistical analyses prior to study initiation and agreed that these documents adequately addressed the objectives necessary to support a regulatory submission for the VMS treatment indication. The key elements of the Phase 3 studies are consistent with the design used for evaluating HT for VMS (US FDA Guidance for Industry, January 2003).

In agreement with the FDA, Noven also conducted a Phase 1 pharmacokinetic study assessing single and multiple doses of LDMP to characterize the pharmacokinetics of paroxetine mesylate 7.5 mg in postmenopausal women. The results were consistent with those obtained previously during the pharmacokinetic characterization of higher doses of paroxetine (**see** Appendix A).

Efficacy

The efficacy of LDMP was established in 2 randomized, double-blind, placebo-controlled Phase 3 studies (N30-003 and N30-004). The studies enrolled 614 and 570 patients, respectively, for a total of 1184 postmenopausal women in the US who met the hot flash eligibility criteria, ie, they had at least 50 moderate to severe hot flashes per week or at least 7 per day on average prior to randomization. Women who met the hot flash eligibility criteria were randomized to receive 7.5 mg of LDMP or placebo once daily at bedtime for 12 weeks (Study N30-003) or 24 weeks (Study N30-004).

In keeping with the FDA guidance document for trial design, each pivotal study was designed to have 4 co-primary endpoints assessing reduction in the *frequency* and in the *severity* of VMS relative to baseline at Week 4 and at Week 12 (US FDA Guidance for Industry, January 2003). Participants recorded the number and severity (ie, mild, moderate, or severe) of daily hot flashes in electronic daily diaries. The statistical criteria for each of the coprimary endpoints for each study ($p \leq 0.05$) were to be met.

The pivotal analyses are based on the set of patients initiating study intervention, and this analysis set is designated as the modified intent-to-treat (mITT) population. Of the 614 patients randomized in Study N30-003, 606 initiated study intervention, with 3 patients in the placebo arm and 5 patients in the LDMP arm not initiating study intervention. Of the 570 patients randomized in Study N30-004, 568 initiated study intervention, with 1 patient in each arm not initiating study drug. Thus the difference between the all randomized and the mITT is small and nearly equal between the arms. Since these studies were double blind there is no expectation of bias resulting from the use of the mITT population.

As is the reality for any longitudinal study, there are missing data. This Executive Overview focuses on completer analyses in the mITT population. In Study N30-003, 89.9% and 87.7% of patients had Week 12 assessments, and in Study N30-004, 86.6% and 90.5% of patients had Week 12 assessments in the control and experimental arms, respectively. It will be shown

subsequently that alternative methods of analyses addressing the impact of missing data do not lead to different conclusions (see Section 3.1.6**)**.

Additional key supportive analyses included assessment of persistence of benefit at Week 24 in Study N30-004 and assessment of the clinical meaningfulness of daily hot flash reduction using the Patient Global Impression of Improvement (PGI-I) scale in Study N30-003.

Efficacy results of the Phase 3 studies

The efficacy results of the Phase 3 studies are displayed in **Table 0-1**. In Study N30-003, 606 patients (301 patients treated with LDMP and 305 with placebo) and in Study N30-004, 568 patients (284 patients treated with LDMP and 284 with placebo) were included in the mITT population. The data from the Phase 3 study endpoints did not meet the normality assumption; therefore, as pre-specified in the Statistical Analysis Plan, nonparametric analysis using rank transformed analysis of covariance (ANCOVA) with baseline as the covariate in the model was conducted and daily medians are reported.

Co-primary endpoints

Daily hot flash frequency

The total number of moderate and severe hot flashes per day was calculated as the sum of moderate and severe hot flashes recorded in the daily hot flash diary each week divided by 7.

Each of the Phase 3 studies showed statistically significant reductions in the frequency of moderate to severe hot flashes relative to baseline with LDMP treatment compared with placebo at Week 4 and Week 12 (**Table 0-1**). In Study N30-003, women taking LDMP had a median daily reduction from baseline of 4.29 hot flashes (versus 3.14 with placebo) at Week 4 ($p<0.0001$) and of 5.93 hot flashes (versus 5.00 with placebo) at Week 12 ($p=0.0090$).

In Study N30-004, the LDMP-treated arm had a median daily reduction from baseline of 3.79 hot flashes (versus 2.50 with placebo) at Week 4 ($p<0.0001$) and 5.57 hot flashes (versus 3.86 with placebo) at Week 12 ($p=0.0001$). In N30-004, the difference in hot flash frequency reduction between LDMP and placebo was statistically significant at Week 24 ($p=0.0021$). A detailed discussion of the reduction in hot flash frequency is provided in Section 3.3.3.

Daily hot flash severity

The reduction in hot flash severity with treatment was determined using a severity score, computed from the diary data. The severity score used in the LDMP program is based on FDA requirements and precedent set by clinical studies of approved hormone therapies for the treatment of moderate to severe VMS. This severity score is computed for each patient for each day by weighting the sum of hot flashes by their relative severity and then dividing this numerator by the total number of hot flashes. The formula is:

Daily Severity Score = $[(2 \cdot F_m + 3 \cdot F_s)] / [(F_m + F_s)]$

Where:

- F_m = Frequency of moderate hot flashes, and
- F_s = Frequency of severe hot flashes.

The reduction in hot flash severity with LDMP compared with placebo was statistically significant at Week 4 in both studies and at Week 12 in Study N30-004 (**Table 0-1**). In Study N30-003, the reduction in hot flash severity at Week 12 numerically favored LDMP but did not reach statistical significance.

In Study N30-003, women taking LDMP had a median daily hot flash severity reduction from baseline of 0.052 (versus 0.000 with placebo) at Week 4 (p=0.0017) and of 0.058 (versus 0.018 with placebo) at Week 12 (p=0.1658).

In Study N30-004, the LDMP-treated arm had a median daily reduction in hot flash severity from baseline of 0.040 (versus 0.008 with placebo) at Week 4 (p=0.0368) and 0.051 (versus 0.000 with placebo) at Week 12 (p=0.0064). In Study N30-004, the difference in the severity score between LDMP and placebo was statistically significant at Week 24 (p=0.0320). A detailed discussion of the reduction in hot flash severity is provided in Section 3.3.3.

Table 0-1 Results of co-primary endpoints in LDMP Phase 3 trials

	Week 4			Week 12		
	Change from Baseline			Change from Baseline		
	Placebo	LDMP	P value	Placebo	LDMP	P value
Study N30-003: Co-primary endpoints						
Reduction in daily hot flash frequency (median), ranked ANCOVA	n = 293 -3.14	n = 289 -4.29	<0.0001	n = 274 -5.00	n = 264 -5.93	0.0090
Reduction in daily hot flash severity (median), ranked ANCOVA	n = 289 0.000	n = 281 -0.052	0.0017	n = 253 -0.018	n = 236 -0.058	0.1658
Study N30-004: Co-primary endpoints						
Reduction in daily hot flash frequency (median), ranked ANCOVA	n = 274 -2.500	n = 276 -3.786	<0.0001	n = 244 -3.857	n = 257 -5.571	0.0001
Reduction in daily hot flash severity (median), ranked ANCOVA	n = 271 -0.008	n = 268 -0.040	0.0368	n = 236 0.000	n = 245 -0.051	0.0064

Rank transformed analysis of covariance (ANCOVA), with baseline as a covariate in the model.

Supportive endpoints

Persistence of benefit

Persistence of benefit was assessed by showing a statistically significant difference of 50% or more reduction at Week 24 compared to baseline between the LDMP and placebo treatment arms. The logit model was used to analyze the proportion of patients in each arm who had a 50% or more reduction in hot flash frequency relative to baseline with baseline number of hot flashes as a covariate in the model.

In Study N30-004, persistence of benefit of LDMP extended to Week 24, as demonstrated by the supportive endpoint. More patients treated with LDMP than placebo (47.5% versus 36.3%; p=0.0066) had a ≥50% reduction in frequency of moderate to severe hot flashes at Week 24. A detailed discussion of this analysis is provided in Section 3.3.5.

Clinical meaningfulness anchored to patient-reported improvement

The magnitude of the effect size of the frequency change primary endpoint can be referred to other outcomes in order to gain a broader understanding of the effect size observed for the primary endpoint. For example, the PGI-I scale (Appendix L) is a patient-reported outcome (PRO) that is widely accepted as reflecting a patient's improvement as a result of an intervention in clinical trials. In Study N30-003, which used the PGI-I, a method based on the receiver operating characteristic (ROC) model was used to relate the frequency change effect size to the results from the PGI-I as an anchor. Patients were considered to be clinically improved if their PGI-I score was less than or equal to 3 (3 = a little better; 2 = much better; 1= very much better). This PGI-I cut-off was used to classify patients into a dichotomy of "improved" versus "not improved." Using this dichotomy, the ROC analysis was used to derive an optimal cut-off for the frequency change primary endpoint and this frequency change cut-off was used to classify patients as responders versus nonresponders relative to the frequency change primary endpoint. A between-arm analysis of this frequency change response outcome was then performed.

There were significantly more responders in the LDMP group compared with the placebo group at Week 4 (58.5% LDMP, 47.2% placebo; p=0.0058). At Week 12, 47.8% of LDMP-treated patients were responders, compared with 41.6% of those receiving placebo (p=0.1332). Thus, this ROC analysis relating the PGI-I to the frequency change primary outcome demonstrates directional favorability for the LDMP arm for the cut-off derived. A detailed discussion of the methodology for this analysis is provided in Section 3.1.8.1.

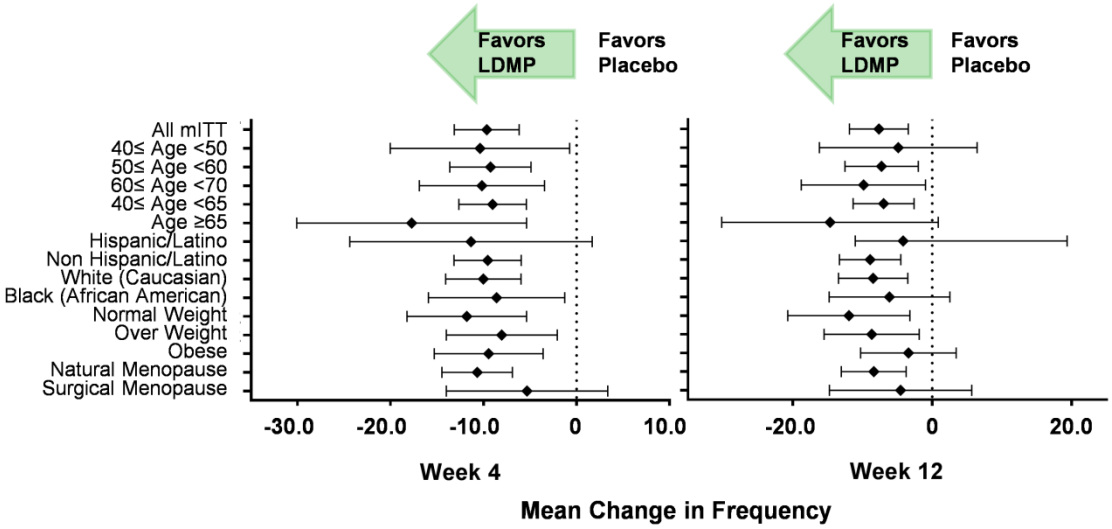
Additional analyses directed at assessing clinical meaningfulness of the demonstrated effects of LDMP treatment on moderate to severe VMS were conducted using prespecified secondary endpoints **(**Appendices F and G**)**. More LDMP-treated patients reported feeling either "much better" or "very much better" on the PGI-I scale compared with placebo-treated patients in the N30-003 study (see Section 3.3.7). In both studies, women treated with LDMP had significantly

fewer nighttime awakenings compared with the placebo group, and this effect appeared to improve over time (see Section 3.3.8).

Effect modification analyses

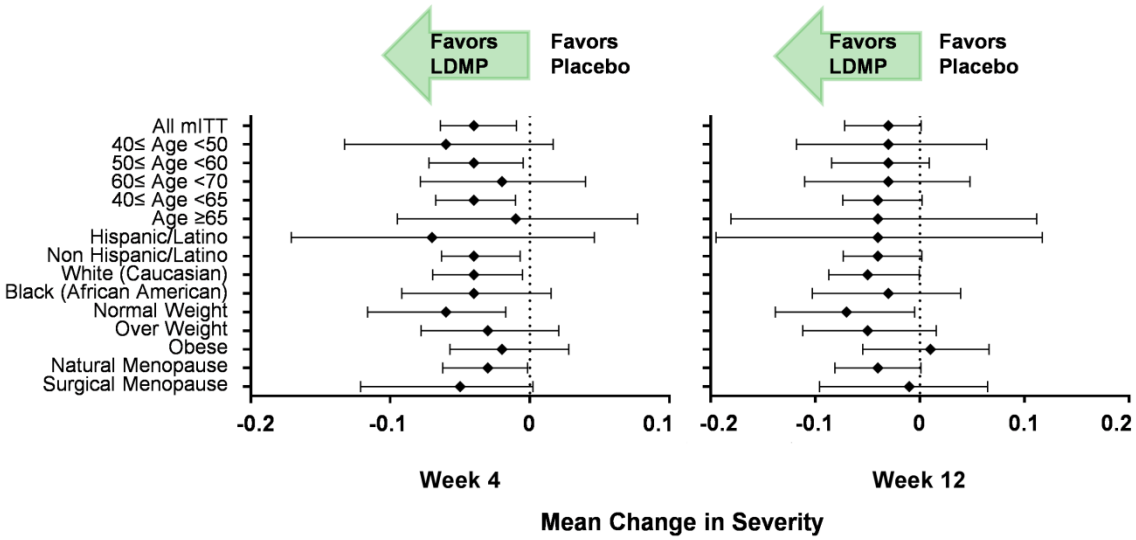
Effect modification analyses for the baseline attributes were conducted based on age, race, ethnicity, BMI, and type of menopause onset in the pooled mITT populations of the N30-003 and N30-004 studies. Results of these effect modification analyses are shown in the following forest graphs for the mean change in hot flash frequency (**Figure 0-1**) and severity (**Figure 0-2).** These analyses provide evidence of general effect consistency across the baseline attributes analyzed.

Figure 0-1 Effect modification analyses of mean frequency change (95% CI) in moderate to severe hot flashes at Week 4 and Week 12, mITT Population, Pooled Phase 3 Studies



CI=confidence intervals; mITT=modified intent-to-treat.

Figure 0-2 Effect modification analyses of mean severity change (95% CI) in moderate to severe hot flashes at Week 4 and Week 12, mITT Population, Pooled Phase 3 Studies



CI=confidence intervals; mITT=modified intent-to-treat.

Consistency of LDMP effect across multiple outcomes – Exploratory analyses

Exploratory analyses on the most clinically relevant secondary endpoints, which included change from baseline in total number of awakenings due to hot flashes per day (using sleep diary); change from baseline in climacteric symptoms at Week 12, using the Greene Climacteric Scale (GCS); assessment of interference of hot flashes, using the Hot Flash Related Daily Interference Scale (HFRDIS); proportion of patients with positive PGI-I response; and assessment of mood, using the Profile of Mood States (POMS) questionnaire show a directionality of effect favorable to LDMP, and these results correlate to the findings of the co-primary endpoint analyses.

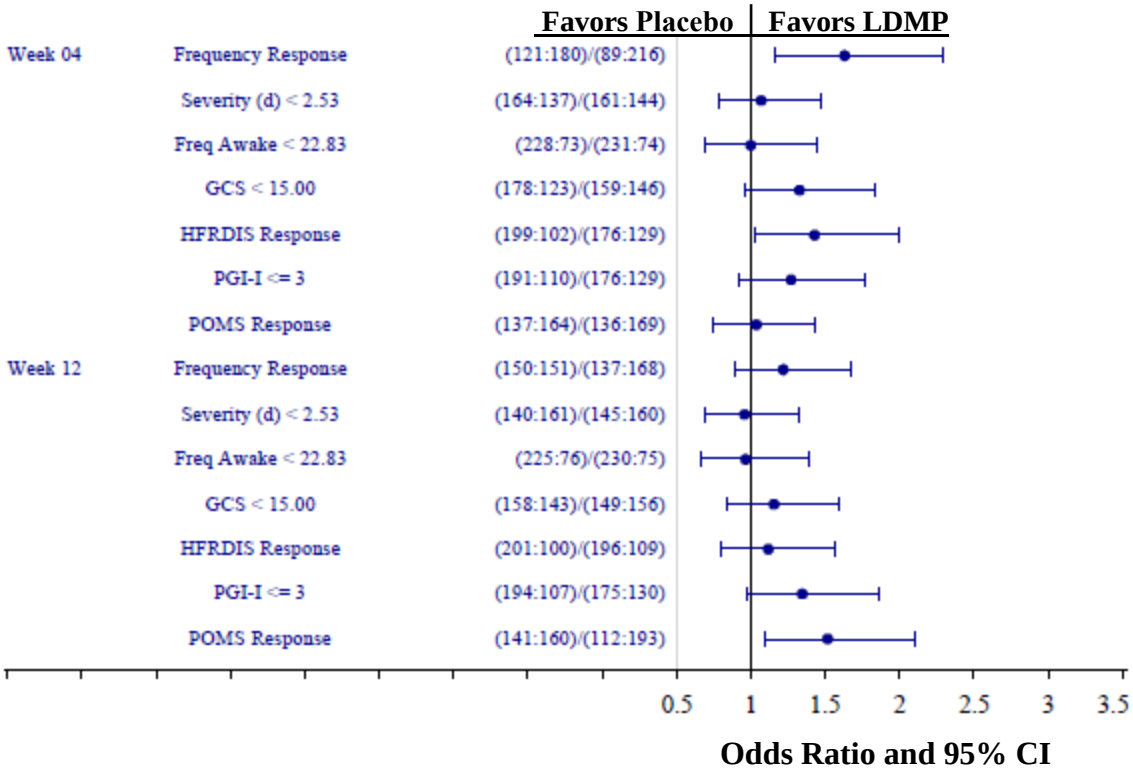
Consistency of direction and magnitude of effect across multiple outcomes provides consensus evidence of LDMP effect. A broader picture of the nature of effect is supported when these outcomes are meaningful and measure different aspects of outcome. In order to be able to illustrate the general effect direction across multiple outcomes, each outcome must be converted to the compatible scales. One simple and readily accessible method used is to assure that each outcome is converted to be expressed as a response dichotomy.

Forest plots of the outcomes for each of these endpoints by study and week are shown in **Figures 0-3** through **0-4** with missing data changed to 'no response," and therefore these analyses are based on the full mITT. These analyses were done using dichotomy with exact methods. For each analysis, the odds ratio estimate and the exact 95% confidence interval was computed. The frequencies associated with each analysis are shown on the graphs; the LDMP arm frequency odds are shown in the numerator and the placebo arm frequency odds are shown in the

denominator. (Note that these exploratory analyses did not have applicable predefined statistical criteria and the study size was not planned based on these analyses.)

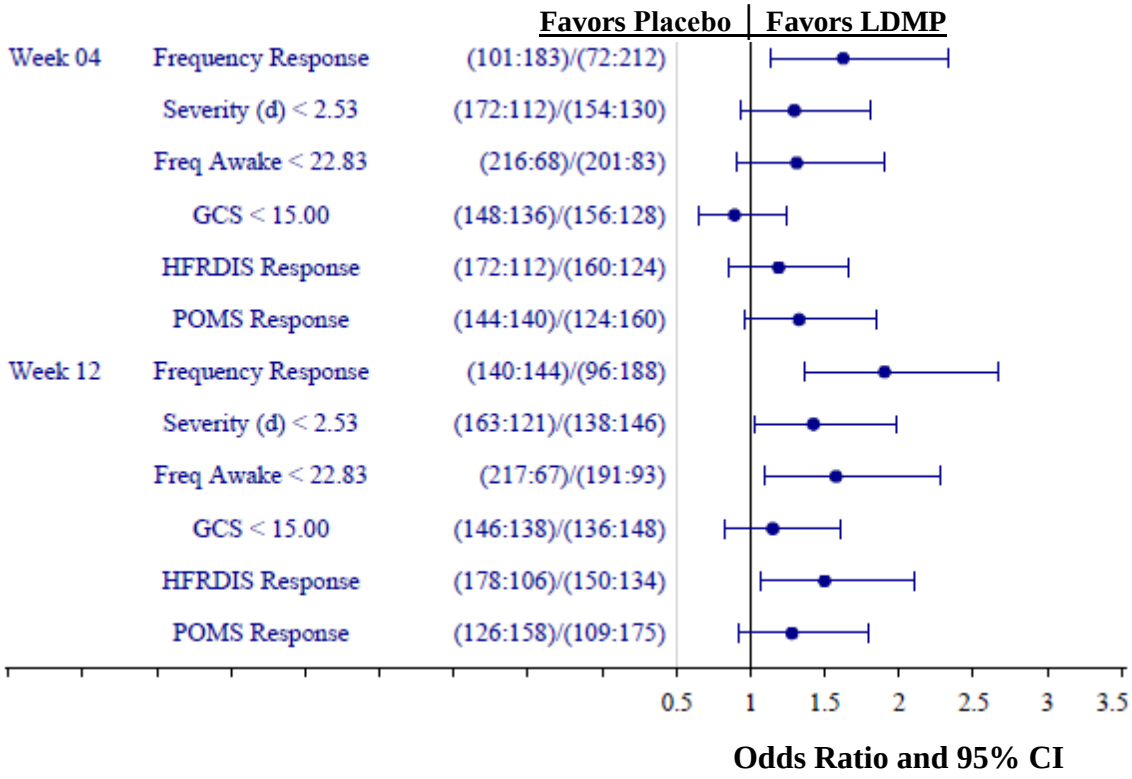
There is general consistency across the outcomes and the information conveyed by the confidence interval, showing that the mITT response finding is generally associated with benefit in these other outcomes.

Figure 0-3 Multiple outcomes by treatment arm at Weeks 4 and 12, mITT Population, Study N30-003



CI=confidence interval; Freq Awake=frequency of nighttime awakenings; Freq response=hot flash frequency reduction; GCS=Greene Climacteric Scale; HFRDIS=Hot Flash-Related Daily Interference Scale; mITT=modified intent-to-treat; PGI=Patient Global Impression of Improvement; POMS=Profile of Mood States; Severity=severity score.

Figure 0-4 Multiple outcomes by treatment arm at Weeks 4 and 12, mITT Population, Study N30-004



CI=confidence interval; Freq Awake=frequency of nighttime awakenings; Freq response=hot flash frequency reduction; GCS=Greene Climacteric Scale; HFRDIS=Hot Flash-Related Daily Interference Scale; mITT=modified intent-to-treat; PGI=Patient Global Impression of Improvement; POMS=Profile of Mood States; severity=severity score.

Safety

In the clinical development program, LDMP 7.5 mg once daily demonstrated a favorable safety profile in the population of patients treated for moderate to severe VMS associated with menopause. Paroxetine has an established safety profile in psychiatric indications at doses ranging from 10 to 60 mg. Paroxetine at currently available doses is used to treat depression in the age group studied in the LDMP clinical development program, including postmenopausal women who may also have VMS. It is also used off-label at higher doses than 7.5 mg to treat VMS in women who are not depressed.

The LDMP NDA was filed under Section 505(b)(2), and therefore relies on FDA's findings of safety for higher doses of paroxetine. No new or unexpected safety findings were observed in the clinical program out to Week 24 with the 7.5 mg dose. The proposed label for LDMP adopts the warnings, precautions, and drug-drug interactions that are described in the product labeling for paroxetine at higher doses.

Adverse events (AEs) of special interest were determined to be those listed as warnings and precautions in the current labeling for higher-dose paroxetine (Paxil PI, Pexeva PI), which include suicidality, gastrointestinal (GI) bleeding or any other bleeding events, and fractures. In addition to the collection of AE data, suicidality, sexual dysfunction, and discontinuation symptoms were prospectively assessed using validated scales. Weight was measured at every clinic visit. Weight gain and sexual dysfunction are AEs associated with higher doses of paroxetine, which could be of particular concern in the postmenopausal population.

AEs associated with LDMP were consistent with the known safety profile of paroxetine, and occurred at a lower incidence than observed in clinical trials for the psychiatric indications, as described in the Paxil and Pexeva labeling (Paxil PI, Pexeva PI).

The overall incidence of AEs was similar across the 2 treatment groups, with 50.4% of LDMP-treated patients and 47.0% of placebo-treated patients reporting at least 1 AE. The only AEs reported in ≥2% of patients in the LDMP arm with at least twice the incidence compared to the placebo arm were nausea, fatigue, and dizziness. The majority of these common events were mild to moderate in severity, occurred in the first weeks of treatment and resolved as treatment continued, and did not result in discontinuation.

One death occurred in the clinical program in the LDMP arm. She was a 55 year-old obese African American woman with a history of uncontrolled hypertension and hypercholesterolemia who presented 68 days after starting the trial with severe arterial hypoxemia and several days of shortness of breath. She was determined to be in acute respiratory failure with evidence of hypertension-mediated pulmonary edema and hypertensive cardiovascular disease. She died of acute respiratory failure, and the death was deemed by the investigator to be unrelated to study drug.

Serious adverse events (SAEs) were reported in 2.2% of patients treated with LDMP and 1.4% with placebo. A total of 3 cardiovascular SAEs were reported, 1 in a patient treated with placebo and 2 with LDMP, both of which occurred in the same patient who died (described above). One suicide attempt (0.2%) and 3 cases of suicidal ideation (0.5%) were reported as SAEs in the LDMP arm, and no suicidality SAEs were reported in the placebo arm (see Section 4.10.2 for additional discussion regarding suicidality).

The incidence of study drug discontinuation due to AEs in the LDMP and the placebo treatment arms was 4.4% and 3.3%, respectively. There was no perceptible pattern to the cause of discontinuations.

In the LDMP arm, there was no increase in mean weight gain, sexual dysfunction, or discontinuation symptoms in patients treated with LDMP compared with placebo. Additional information about safety is provided in Section 4.

A review of the 2012, 2nd quarter (Q2) release of the Adverse Event Reporting System (AERS) database showed that case reports for female paroxetine users aged 40 to 65 years were similar

between the two dosing groups of 10 mg and >10 mg with respect to (i) age; (ii) top 15 indications for use; (iii) menopause-related indications for use; and (iv) primary outcome. When signals of disproportionality were examined, the events of interest for the top 15 scores that met the signal threshold were not remarkably different between the two dosing groups, but the >10 mg group had disproportionality scores that were much higher than those reported for the 10 mg group.

When examining Preferred Terms of interest relating to major cardiovascular events, suicidality, abnormal bleeding, and bone fracture, differences were found between the 10 mg and >10 mg dosing groups with respect to suicidality, with the number and strength of the signals being higher in the >10 mg dose group. No conclusions could be drawn from the abnormal bleeding terms of interest as different signals met the threshold in the different dosing groups. There were no signals that met the significance threshold among the serious cardiac events or the bone fracture-related terms of interest for either dosing group (see Appendix U).

Risk Management

To ensure the appropriate use of LDMP, Noven has developed a risk management plan that will include the following elements: label, medication guide, pharmacovigilance, enhanced pharmacovigilance, education plan, and assessment.

The proposed LDMP label will reflect the SSRI class labeling, including the boxed warning for suicidality. The class Warnings and Precautions describe the safety profile of the full range of psychiatric dosing, which is up to 60 mg per day. The well-characterized drug-drug interaction profile of paroxetine has also been adopted in the proposed label for LDMP. Patients prescribed LDMP will receive a medication guide alerting them to the known risks and precautions associated with the use of paroxetine.

In addition to the pharmacovigilance activity of collecting adverse event data from multiple sources, Noven is also planning to conduct enhanced pharmacovigilance for adverse events of special interest, such as suicidality, abnormal bleeding, and bone fracture. New cases of these events reported with LDMP will be queried for the following elements in an attempt to obtain a complete picture of the event: symptoms experienced and date of onset; clinical outcome; duration of LDMP therapy; start and stop dates for all concomitant medications taken within 6 months of event onset; relevant medical history within the past 10 years. This information will be reviewed for a potential signal and shared with FDA on an ongoing basis.

The Education Plan will target prescribers, pharmacists, and patients. The education content will highlight the potential risks captured in the label and the importance of monitoring patients for these risks. It will include information on the drugs that should not be used concomitantly with LDMP. On an ongoing basis, Noven will assess the appropriateness and effectiveness of risk management activities in consultation with FDA.

Benefit/Risk Assessment

LDMP has a favorable benefit/risk profile for the treatment of moderate to severe VMS associated with menopause. An LDMP 7.5 mg capsule given once daily at bedtime is a lower daily dose of paroxetine than is currently approved for psychiatric indications. The data from the LDMP clinical development program establish the tolerability and efficacy of 7.5 mg paroxetine mesylate for the treatment of VMS.

Clinical benefit

LDMP 7.5 mg/day is a nonhormonal agent containing paroxetine mesylate, developed specifically for the treatment of moderate to severe VMS associated with menopause. The efficacy of LDMP dosed once daily at bedtime has been demonstrated in two pivotal Phase 3 trials including 1184 women with moderate to severe VMS associated with menopause. The results of these studies show statistically significant and clinically meaningful benefit in this patient population.

Statistically significant reduction in hot flash frequency compared to placebo was shown in studies N30-004 and N30-003 at Weeks 4 and 12. Statistically significant reduction in hot flash severity compared to placebo was shown in study N30-004 at Weeks 4 and 12 and in study N30-003 at Week 4.

LDMP treatment demonstrated both rapid onset and persistence of benefit. Persistence of benefit was shown in study N30-004, with significantly more patients treated with LDMP achieving at least a 50% reduction in frequency of moderate to severe hot flashes compared with placebo at Week 24. Analyses of time to onset of hot flash reduction showed significant reductions in frequency of hot flashes in patients treated with LDMP as early as Week 1.

The clinical meaningfulness of the reduction in hot flash frequency with LDMP was supported by the results of an analysis anchored to patient-reported improvement. In addition to the primary and key supportive endpoints, the clinical meaningfulness of the effects of LDMP was further evaluated through a comprehensive set of 19 prespecified secondary analyses. Most notably, LDMP demonstrated improvements compared to placebo at Weeks 4 and 12 in reducing the number of nighttime awakenings due to moderate to severe hot flashes. Exploratory analyses on the most clinically relevant of these endpoints show a directionality of effect favorable to LDMP, and these results correlate to the findings of the co-primary endpoint analyses.

Findings from subgroup analyses of the primary endpoints consistently favored LDMP compared with placebo. Of 70 subgroup comparisons with a sample size of at least 20 patients per group, 65 (93%) of the comparisons were numerically in favor of LDMP. These results support the effectiveness of LDMP 7.5 mg across age categories, race, ethnicity, BMI, and type of menopause onset.

Taken together, these studies provide substantial evidence for the efficacy of LDMP 7.5 mg once daily at bedtime for the treatment of moderate to severe VMS associated with menopause.

Risks

The LDMP clinical trial program demonstrated tolerability and a favorable safety profile in the population of patients treated for moderate to severe VMS associated with menopause. In the context of the established safety database for higher doses of paroxetine prescribed for approved psychiatric indications, no new safety signal was observed with LDMP.

From an analysis of the AERS database, it appears that certain events of interest and signal scores are greater in the cases of female paroxetine users aged 40 to 65 years reported into AERS in the >10 mg dose group compared to the 10 mg dose group (see Appendix U).

The majority of AEs with LDMP were mild to moderate and did not result in discontinuation. Some patients reported nausea, fatigue, and dizziness, most of which occurred early in the first weeks of treatment and resolved as treatment continued.

Sexual dysfunction and weight gain are side effects of special concern to many patients taking SSRIs. In the LDMP clinical program, the incidence of AEs suggestive of sexual dysfunction was similar in the LDMP and placebo groups, and there were no inter-group differences in ASEX scores. There was no evidence of weight gain compared with placebo.

The incidence of study drug discontinuations due to AEs was 4.4% in the LDMP group compared with 3.3% in the placebo group. However, the most frequently reported AEs resulting in study drug discontinuation in the LDMP group occurred in only 2 patients (0.3%) each. There was no clinically relevant difference in laboratory evaluations, vital signs, body weight, body mass index, or electrocardiograms between the LDMP and placebo groups.

The proposed LDMP label will include the full warnings and precautions of higher-dose paroxetine products. Noven will also have a careful risk management strategy in place post-marketing for potential risk factors such as suicidality, abnormal bleeding, and bone fractures. Prescribing physicians will need to keep these in mind when considering this treatment option.

Conclusions

There is an unmet medical need for additional treatment options for women seeking treatment of their moderate to severe VMS associated with menopause. Currently, HT is the only approved treatment for VMS associated with menopause. Although HT is effective, there are some women who are unable or unwilling to take HT. Additional, FDA-approved treatment options are needed for women seeking treatment and for physicians.

LDMP is a nonhormonal agent that has demonstrated efficacy out to 24 weeks and a favorable safety and tolerability profile. If approved, LDMP would represent an important new treatment option that may improve the lives of women with moderate to severe VMS.

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LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviation	Definition
AE	Adverse event
AERS	Adverse Event Reporting System
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASEX	Arizona Sexual Experience Scale
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
bpm	Beats per minute
C-CASA	Columbia Classification Algorithm for Suicide Assessment
CGI	Clinical Global Impression
CI	Confidence interval
$C_{avg,ss}$	Average plasma concentration during the dosing interval calculated as $AUC_{0-\tau}/\tau$, where $\tau = 24$ hours
C_{max}	Maximum plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval (0-24 hours)
CNS	Central Nervous System
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DESS	Discontinuation-emergent signs and symptoms
DDI	Drug-drug interactions
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCS	Greene Climacteric Scale
GEE	Generalized Equation Estimation
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone.
HADS	Hospital Anxiety and Depression Scale
HFRDIS	Hot Flash Related Daily Interference Scale
HT	Hormone therapy
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDMP	Low-Dose Mesylate Salt of Paroxetine
LH	Luteinizing hormone
LOCF	Last observation carried forward
MAOI	Monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat

Abbreviation	Definition
MMRM	Mixed model repeated measure
MOA	Mechanism of action
n	Number of observations
N	Number in the population and treatment group
NDA	New Drug Application
NEC	Not elsewhere classified
NOS	Not otherwise specified
NRS	Numerical Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
PGI-I	Patient Global Impression of Improvement
PI	Prescribing information
PK	Pharmacokinetic
POMS	Profile of Moods State
PRO	Patient-reported outcome
PRR	Proportional reporting ratio
PSQ	Patient Satisfaction Questionnaire
Q2	Second quarter
RLD	Reference listed drug
ROC	Receiver operating characteristic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAQ	Symptom assessment questionnaires
SD	Standard deviation
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOC	System organ class
SPA	Special Protocol Assessment
SSRI	Selective serotonin reuptake inhibitor
STS	Suicidality Tracking Scale
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
USPI	United States package insert
VMS	Vasomotor symptoms

1 INTRODUCTION

This document summarizes the rationale and evidence supporting consideration of paroxetine 7.5 mg referred to as Low-Dose Mesylate Salt of Paroxetine (LDMP) for the following indication:

LDMP is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

LDMP is a nonhormonal drug specifically developed for the treatment of moderate to severe VMS associated with menopause. The LDMP capsule contains 9.69 mg of paroxetine mesylate, equivalent to 7.5 mg of paroxetine base. LDMP is a selective serotonin reuptake inhibitor (SSRI) and its mechanism of action for the treatment of VMS is thought to be related to the potentiation of neurotransmitters in the central nervous system that affect regulation of body temperature control (Bachmann 2005, Rossmanith and Ruebberdt 2009) (see Appendix A).

LDMP is administered as a 7.5 mg capsule taken once daily at bedtime. Paroxetine mesylate was approved by the United States Food and Drug Administration (US FDA) in 2003 at doses ranging from 10 to 60 mg daily for the treatment of major depressive disorder, obsessive compulsive disorder, and panic disorder with or without agoraphobia, and in 2006 it was approved for generalized anxiety disorder. Noven markets a paroxetine mesylate product under the trade name PEXEVA®. Paroxetine hydrochloride, which is the same active ingredient formulated with a different salt, has been approved since 1992 for multiple psychiatric indications under the trade name Paxil.

1.1 Menopause and associated symptoms

Menopause is a natural part of a woman's life, commonly defined as 12 months of amenorrhea. This transition often begins in the late 40s, with a median age of 51 years. Menopause is associated with many symptoms including VMS, vaginal symptoms, urinary incontinence, sexual dysfunction, difficulty concentrating, mood swings, joint pain, and trouble sleeping (Pachman et al 2010; Woods et al 2011).

VMS, also referred to as hot flash or hot flush, is the most common symptom among women entering menopause and occurs in up to 75% of menopausal women (Feldman et al 1985). Hot flashes are a spontaneous sensation of warmth associated with perspiration, anxiety, and palpitations (Nelson et al 2006), which may occur only weekly or monthly or as frequently as daily or hourly. In many women, VMS is severe enough to interrupt their daily personal and professional activities and prevent a full night's sleep (Fugate and Church 2004; Nelson et al 2006; Pachman et al 2010; Rapkin 2007). VMS may also interfere with relationships at home or work (Woods et al 2011). These wide-ranging effects on quality of life indicate that there is no single, simple approach to assessing the effectiveness and clinical meaningfulness of treatment for VMS.

Hot flash episodes usually last for 2 to 4 minutes. Onset of hot flashes most commonly occurs during the first 2 years following menopause, and the majority of women experience symptoms for 6 months to 2 years (Utian 2005; Warren 2010).

The US FDA defines moderate VMS as sensation of heat with sweating and ability to continue activity; severe VMS is defined as sensation of heat with sweating, causing cessation of activity. The definition of mild VMS is a sensation of heat without sweating (US FDA Guidance for Industry, January 2003).

1.2 Unmet medical need

The only current FDA-approved treatment option for VMS is hormone therapy (HT). The prescribing information for HT lists contraindications for women with a history of breast or estrogen-dependent neoplasia. Many women are reluctant to take HT because of perceived risks.

Given the limitations of HT both in terms of physician use and patient acceptance, some physicians prescribe neuropsychiatric drugs, including SSRIs, serotonin-norepinephrine receptor inhibitors (SNRIs), gabapentin, and clonidine, off-label to treat VMS. These drugs which are prescribed off-label lack the approved prescribing information label to guide appropriate use in VMS.

Each year women 40 to 65 years old receive 4.5 million prescriptions of paroxetine for approved indications. In the past year, 3.3 million prescriptions were filled for SSRIs and SNRIs to treat VMS. Of these prescriptions, 2.4 million were for SSRIs and more than 250,000 were for paroxetine. The most common dosage strengths of paroxetine prescribed off-label for VMS were 20 mg (112,000 prescriptions) and 40 mg (52,700 prescriptions) (IMS NPA Market Dynamics™ for the period December 2011 to November 2012).

Selective serotonin reuptake inhibitors (including paroxetine) are approved treatments for psychiatric disorders such as depression. In the 1990s, it was recognized that women taking SSRIs had a decrease in hot flashes (Shanafelt et al 2002) associated with menopause. As a result of these observations, it was hypothesized that such compounds may have a therapeutic effect on hot flashes if specifically used as an intervention for symptomatic menopausal patients.

At present, no SSRI is approved for the treatment of moderate to severe VMS associated with menopause, and no guidance exists for the development of SSRIs for this indication. In the absence of approved nonhormonal compounds, there remains an unmet need for an FDA-approved nonhormonal therapy for the treatment of moderate to severe VMS associated with menopause that has demonstrated efficacy and tolerability in this population.

1.3 Development history

Noven sought to develop a new nonhormonal treatment for moderate to severe VMS. The company began with a literature search for existing drugs with evidence of effectiveness in treating VMS.

Paroxetine had been found to be effective for the treatment of VMS at higher doses in several small pilot studies (Stearns et al 2000, Stearns et al 2003a) and was among the most effective SSRIs studied for this condition (Loprinzi et al 2009). Across the dose range studied there was no dose relationship for efficacy, but there was a dose relationship for tolerability. Of particular interest is a randomized, placebo-controlled, 6-week Phase 2 study in which controlled-release paroxetine at doses of 12.5 mg/day and 25 mg/day was assessed in a general population of menopausal women (Stearns et al 2003a). Both doses of paroxetine were more effective than placebo with regard to the change from baseline to Week 6 in daily hot flash composite score, and both doses were associated with a similar magnitude of hot flash reduction. The adverse events (AEs) most frequently reported for paroxetine were headache, nausea, and insomnia, with fewer reports overall from patients receiving the lower dose of paroxetine compared with the higher dose. Based on the information in the literature, Noven hypothesized that a product with a paroxetine dose lower than those prescribed for psychiatric disorders could be effective for treating VMS while having a lower incidence of the side effects, such as weight gain, sexual dysfunction, and discontinuation symptoms, which could be a concern in the VMS population.

Noven has been in dialogue with the FDA throughout the development of LDMP. Because of the well-established safety profile of paroxetine at much higher doses, FDA agreed that Noven could develop this product under the 505(b)(2) pathway, relying on FDA's findings of safety for paroxetine hydrochloride (Paxil) and referencing the nonclinical and clinical pharmacology data previously submitted in the Pexeva New Drug Application (NDA). The Pexeva NDA included studies directly comparing Paxil and Pexeva that demonstrated no difference in toxicity, mutagenicity, or pharmacokinetic (PK) parameters of the two salt forms; therefore, no new nonclinical or safety studies were required during the development of LDMP. **Table 1-1** shows portions of the application that rely on referenced information, as agreed with FDA.

Table 1-1 Application Sections Relying on FDA's Findings of Safety for Paxil/Paroxetine

Data Type	New Studies Conducted to Support LDMP NDA	Reference to Noven Studies Conducted to Support Pexeva	Reliance on Literature or FDA's Findings of Safety for Paxil/Pexeva
Nonclinical	n/a	Comparative studies demonstrating no difference in toxicity, mutagenicity, or PK between mesylate and hydrochloride salt forms of paroxetine ▪ Acute toxicity (intravenous and oral) in mice and rats ▪ Repeat-dose toxicity (14 days orally, dose range-finding study) followed by a full 28-day, oral, subchronic toxicity study in rats ▪ Ames test ▪ Pharmacokinetic animal studies including ADME in nonpregnant rats and AD in pregnant rats	Nonclinical safety studies using high doses of paroxetine in various animal species Mechanism of action
Clinical Pharmacology	Single and repeat-dose PK study: ▪ N30-005	Comparative study bridging mesylate salt to hydrochloride salt	Information on absorption, distribution, metabolism, excretion, drug-drug interactions, and food effects of paroxetine
Clinical Safety	Pivotal studies: ▪ N30-003, N30-004 Phase 2 study: ▪ N30-002 Single and repeat-dose PK study: ▪ N30-005	n/a (proposed label will include relevant warnings, precautions, and contraindications from Pexeva label)	Literature related to safety of paroxetine for treatment of VMS associated with menopause (and other non-psychiatric populations)
Clinical Efficacy	Pivotal studies: ▪ N30-003, N30-004 Phase 2 study: ▪ N30-002	n/a	Literature to support dose selection

AD=absorption and distribution; ADME=absorption, distribution, metabolism, and excretion; n/a=not applicable; NDA=New Drug Application; VMS=vasomotor symptoms.

In 2008, Noven initiated a proof-of-concept Phase 2 study (N30-002) of LDMP in postmenopausal women with moderate to severe VMS. The 7.5 mg dose was chosen because it is substantially lower than the doses of paroxetine used off-label to treat VMS. Results of the Phase 2 study provided proof of concept and showed that the 7.5 mg dose was well tolerated. The results reflected the high placebo response seen in the literature for VMS (Stearns et al 2000, Stearns et al 2003a, MacLennan et al 2004, Stearns 2005, Nedrow et al 2006). This study also informed the estimation of effect size for the Phase 3 development program (see **Table 1-2**).

The Phase 3 program comprised 2 pivotal trials (Study N30-003 and Study N30-004). Both protocols incorporated FDA feedback, and Study N30-003 was conducted under a Special Protocol Assessment (SPA), whereby the FDA reviewed the study design, clinical endpoints, and statistical analyses prior to study initiation and agreed that these documents adequately addressed the objectives necessary to support a regulatory submission for the VMS treatment indication. The key elements of the Phase 3 studies are consistent with the design used for evaluating HT for VMS (US FDA Guidance for Industry, January 2003). In agreement with the FDA, Noven also conducted a Phase 1 pharmacokinetic study assessing single and multiple doses of LDMP to characterize the pharmacokinetics of paroxetine mesylate 7.5 mg in postmenopausal women.

Table 1-2 Description of LDMP clinical studies

Study ID	No. of Centers Location	Study Dates Start–Completion	Total Enrollment Planned/ Actual	Study Design Control Type	Dose, Route, and Regimen	No. of Patients by Arm Entered/ Completed	Duration	Median Age (Range)	Diagnosis Inclusion Criteria
Clinical Pharmacology - Phase 1									
N30-005	1 US	15 July 2011–12 August 2011	24/24	Phase 1, open-label, single-center, single- and repeat-dose (14 days), uncontrolled	LDMP 7.5 mg capsules, daily oral dose	LDMP 24/24	3 weeks screening, 1 day treatment (followed by 5 nontreatment days), then 14 days treatment	55 years (45-72)	≥40 years healthy postmenopausal women
Proof-of-concept - Phase 2									
N30-002	10 US	29 October 2008–26 May 2009	90/102	Phase 2, exploratory, 8-week, multicenter, double-blind, randomized, placebo-controlled	LDMP 7.5 mg capsules versus placebo, daily oral dose	LDMP 49/45 Placebo 52/51	1 week placebo run-in period, 8 weeks treatment	55 years (40-67)	≥40 years postmenopausal women reporting moderate to severe hot flashes
Pivotal Studies - Phase 3									
N30-003	70 US	6 June 2011–3 January 2012	534/614	Phase 3, 12-week, multicenter, double-blind, randomized, placebo-controlled	LDMP 7.5 mg capsules versus placebo, daily oral dose	LDMP 306/271 Placebo 308/278	7 days screening, 12-day placebo run-in period, 12 weeks treatment	54 years (40-79)	≥40 years postmenopausal women reporting moderate to severe hot flashes
N30-004	65 US	30 March 2010–12 September 2011	534/570	Phase 3, 24-week, multicenter, double-blind, randomized, placebo-controlled	LDMP 7.5 mg capsules versus placebo, daily oral dose	LDMP 285/235 Placebo 285/218	7 days screening, 12-day placebo run-in period, 24 weeks treatment	54 years (40-74)	≥40 years postmenopausal women reporting moderate to severe hot flashes

LDMP=Low-Dose Mesylate Salt of Paroxetine; US=United States.

2 PHARMACOKINETICS OF LDMP

The pharmacokinetics and metabolism of paroxetine following oral administration, and their relevance to drug-drug interactions (DDIs), have been well characterized in the literature and are reported in Appendix A. A Phase 1 single- and multiple-dose PK study (Study N30-005) in postmenopausal women was conducted to characterize the pharmacokinetics of paroxetine mesylate 7.5 mg. This study demonstrated that upon multiple dosing, LDMP exhibits nonlinear pharmacokinetics and extent of accumulation was consistent with data in the published literature and data described in the Pexeva label (see Appendix A).

3 EFFICACY

3.1 Phase 3 studies N30-003 and N30-004 – Overview of study designs and populations

In the clinical development program, LDMP demonstrated efficacy for the treatment of moderate to severe VMS associated with menopause. A proof-of-concept Phase 2 study (N30-002) was conducted in postmenopausal women with moderate to severe hot flashes. Results of the Phase 2 study showed a greater reduction in the frequency and severity of moderate to severe hot flashes with LDMP compared to placebo (Appendix B) and LDMP was well tolerated. The study also provided the estimation of effect size for the Phase 3 development program. A notable effect of placebo treatment was seen in the proof-of-concept N30-002 study despite a 7-day run-in period. This observation is consistent with reports of trials of other nonhormonal treatments for VMS as well as hormonal treatments. A high placebo effect is a common finding in the literature and was reported as efficacious in the treatment of VMS in up to half of postmenopausal women in some studies (Stearns et al 2000, Stearns et al 2003a, MacLennan et al 2004, Stearns 2005, Nedrow et al 2006).

The Phase 3 program comprised two pivotal studies (N30-003, N30-004), which enrolled 614 and 570 patients respectively, for a total of 1184 postmenopausal women in the US who met the hot flash eligibility criteria, ie, they had at least 50 moderate to severe hot flashes per week or at least 7 per day on average prior to randomization. In these studies, LDMP showed a statistically significant benefit in the reduction of hot flash frequency and in the reduction in hot flash severity at most time points analyzed compared with placebo. The treatment effect of LDMP relative to placebo was evident within 1 week after starting therapy and persisted to Week 24. The reduction in hot flash frequency with LDMP was also demonstrated to be clinically meaningful to patients (Study N30-003), and the clinical meaningfulness of these results are further supported by other prespecified secondary endpoints that showed significant improvement with treatment, and an association with the co-primary endpoints of frequency and severity was also demonstrated by exploratory sensitivity analyses.

3.1.1 Phase 3 Study design

The two Phase 3 studies (N30-003 and N30-004) were designed in accordance with the FDA guidance document for trial design in this category (US FDA Guidance for Industry, January 2003). The studies had similar designs: both were US-based, multicenter, randomized, double-blind, placebo-controlled studies of LDMP versus placebo taken once daily at bedtime in postmenopausal women with moderate to severe VMS associated with menopause; however, the study duration was 12 weeks in Study N30-003 and 24 weeks in Study N30-004 (**Figure 3-1**).

Study population: Females, aged 40 or more years, with moderate to severe VMS meeting the hot flash eligibility criteria.

Hot flash eligibility criteria: Patients reporting on average more than 7 moderate to severe hot flashes per day or 50 moderate to severe hot flashes per week prior to randomization.

VMS is defined as:

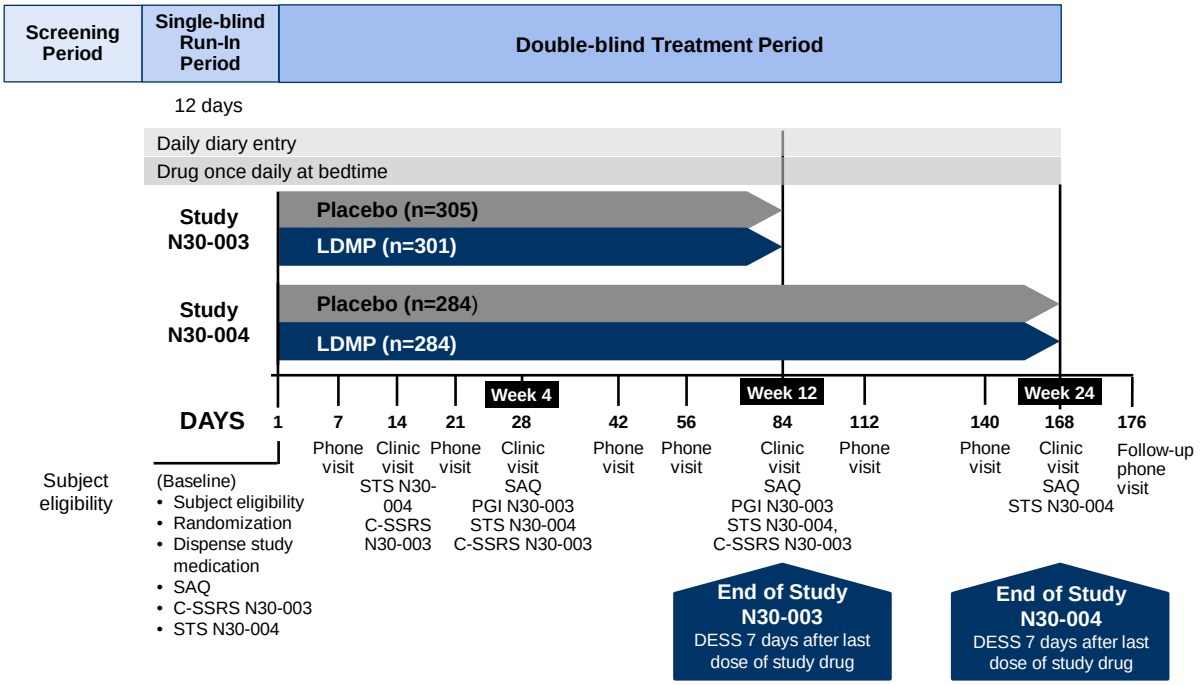
- Mild VMS: sensation of heat without sweating
- Moderate VMS: sensation of heat with sweating, able to continue activity
- Severe VMS: sensation of heat with sweating, causing cessation of activity

Single-blind, placebo, run-in period: In an attempt to reduce the placebo effect seen in the Phase 2 study and to randomize only those patients who met the hot flash eligibility criteria, the placebo run-in period was extended to 12 days in the Phase 3 program. Prior to randomization, patients entered into a 12-day, single-blind placebo run-in period. During the run-in period, patients took placebo once daily at bedtime and were instructed to complete daily hot flash and sleep diaries to record the number of hot flashes experienced daily, the severity of each episode of hot flash, and total number of awakenings due to hot flashes. The 12-day placebo run-in period was included to ensure that patients met the hot flash eligibility criteria and to discontinue patients who were unwilling or unable to complete the electronic diary or who were noncompliant with study medication.

Double-blind treatment period: Following completion of the run-in period, patients who continued to meet hot flash eligibility criteria and were compliant with daily diary entry and with dosing were randomized in a 1:1 ratio to receive either LDMP or placebo administered once daily at bedtime beginning on Day 1 and continuing up to Day 84 for Study N30-003 and from Day 1 to Day 168 for Study N30-004. During the treatment period, patients continued to complete the daily hot flash and sleep diaries. Patients returned to the clinic for evaluations on Day 14 + 3 days, Day 28 + 3 days, Day 85 + 3 days, and Day 169 + 3 days or upon early discontinuation. Site personnel were to contact patients by telephone on Day 7 + 3 days, Day 21 + 3 days, Day 42 + 3, and Day 56 + 3 days. Symptom assessment questionnaires were administered at baseline and on the Day 28, Day 85, and Day 169 visits. Patients were asked to

complete a Discontinuation Emergent Signs and Symptoms Scale (DESS) within 7 ± 3 days after the last dose of study medication.

Figure 3-1 N30-003 and N30-004 study designs



C-SSRS=Columbia-Suicide Severity Rating Scale; DESS=Discontinuation Emergent Signs and Symptoms Scale; SAQ= symptom assessment questionnaires including Arizona Sexual Experience scale (ASEX), Clinical Global Impression (CGI), Greene Climacteric Scale (GCS), Hospital Anxiety and Depression Scale (HADS), Hot Flash-Related Daily Interference Scale (HFRDIS), Numerical Rating Scale (NRS), Patient Global Impression of Improvement scale (PGI-I), Profile of Moods State (POMS), Patient Satisfaction Questionnaire (PSQ), and Suicidality Tracking Scale (STS).

3.1.2 Main study entry criteria

Key inclusion criteria: Postmenopausal women at least 40 years of age with >7 to 8 moderate to severe hot flashes per day on average or 50 to 60 per week for ≥30 days prior to the screening visit were enrolled if 1 of the following criteria for menopause was met: spontaneous amenorrhea for ≥12 consecutive months; amenorrhea for ≥6 months with follicle-stimulating hormone >40 mIU/mL; or bilateral salpingo-oophorectomy, with or without documented hysterectomy, ≥6 weeks before screening. No concomitant estrogen/progestin-containing products were permitted during the study and participants who were taking such products at the screening visit underwent washout periods: 1 week prior to run-in visit for vaginal hormonal products (rings, creams, gels), 4 weeks for transdermal estrogen or estrogen/progestin products, 8 weeks for oral estrogen or estrogen/progestin therapy. No concomitant psychotropic drugs were permitted during the study. Participants who were taking such medications at the screening visit underwent washout periods:

2 weeks before run-in visit for thioridazine, pimozide, tricyclic antidepressants, SSRIs (with the exception of fluoxetine), SNRIs, lithium and oral neuroleptics, and all sedatives and hypnotics (with the exception of zolpidem, zaleplon, eszopiclone, and diphenhydramine); 4 weeks before run-in visit for fluoxetine, Saint John's Wort, and monoamine oxidase inhibitors; and 12 weeks before run-in visit for depot neuroleptics. Participants were not permitted to take the following during the study: tamoxifen; psychotropic drugs; thioridazine; pimozide; monoamine oxidase inhibitors (MAOIs); estrogen or estrogen/progestin-containing products; gabapentin and pregabalin; soy and soy-based products; isoflavone-containing substances; and alternative therapies to treat VMS.

Key exclusion criteria: Patients with a history of hypersensitivity or adverse reaction to paroxetine, nonresponse to previous SSRI or SNRI treatment for VMS, or a history of psychiatric disorders or drug or alcohol abuse were excluded. Patients with evidence of impaired liver or kidney function, uncontrolled hypertension, unstable cardiac disease, biliary tract disease, or thyroid disease were ineligible. Patients taking MAOIs, thioridazine, or pimozide were excluded from Study N30-004, and MAOIs had to be discontinued for at least 4 weeks prior to the run-in visit to qualify for enrollment in Study N30-003. In addition, patients with body mass index (BMI) ≥40 kg/m² were ineligible for Study N30-004.

3.1.3 Use of electronic diary to record daily hot flashes and nighttime awakenings

Patient entered their hot flash data into an electronic diary via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The electronic hot flash diary system was a real-time system compliant with the FDA Guidance for Industry documents of January 2002, August 2003, May 2007, and December 2010. Electronic hot flash diaries were used to (i) reduce the opportunity for transcription errors; (ii) promote real time entry of electronic source data by the patients; and (iii) ensure the accuracy and completeness of data through the use of electronic prompts for missing and inconsistent data. The electronic diary was the source document for the co-primary endpoints.

The electronic diary was available to the patients 24/7 for hot flash data entry. Patients were the authorized data originators for their hot flash data and were provided with individual identifiers (username and password) that allowed access to the IVRS/IWRS system. To establish a clear audit trail, the electronic diary captured the date and time of the data entry and could also identify data from individual patients. To enable a thorough daily review of data, the IVRS/IWRS system generated daily compliance reports for each patient. The compliance reports tabulated the date and time of each hot flash entry and the number of hot flashes entered at each time point. Investigators were required every day to review these daily compliance reports for compliance and completeness. Noncompliant patients were contacted by the site personnel and re-trained. Investigators were required to sign and date the daily compliance reports and maintain a file of these reports. Each study site was also required to maintain a list of all the patients at

their site who were authorized to enter their hot flash data into the IVRS/IWRS system. The list included the patient number and the period for which the patient is authorized to enter data.

The IVRS/IWRS electronic daily hot flash diary and daily sleep diary used for the Phase 3 program had been successfully implemented in the Phase 2 study. Data obtained in the Phase 2 study were interpretable and patients entered data accurately in real-time. As in the Phase 2 study, patients in the Phase 3 studies who were not compliant with diary entries during the run-in period were not eligible for randomization. At the beginning of the study and at each clinic visit, patients were instructed on how to use the system and how to complete the diary accurately and consistently. During the informed consent process, patients were provided with the definitions of mild, moderate, and severe hot flashes which enabled them to determine the severity of their hot flashes (Appendix C). At each clinic visit, site personnel reviewed the definitions of mild, moderate, and severe hot flashes.

3.1.4 Phase 3 sample size calculation

Sample size calculations for the Phase 3 studies were based on the required statistical power of the co-primary VMS frequency and VMS severity endpoints.

The statistical software nQuery 6.01 was used to calculate sample size. For VMS severity, 155 patients per treatment group were required for 95% power based on a Type I error rate of 0.05 (alpha=0.05, 2-sided), a clinically meaningful reduction of greater than 50% in severity (mean difference 0.17 to 0.08), and the common standard deviation of 0.22. For the co-primary endpoint of VMS frequency, 227 patients per treatment group were required to provide 85% statistical power to detect an average difference between the treatments of 1.41 hot flashes per day based on a Type I error rate of 0.05 (alpha=0.05, 2-sided) and the common standard deviation of 5.

A total of 534 patients (267 per treatment group) were to be randomized in each Phase 3 study (N30-003 and N30-004), taking into account a very conservative 15% premature termination rate, which is more than twice the dropout rate (5.9%) observed in the Phase 2 Study N30-002. A sufficient number of patients were to be screened and entered into the run-in period in order to randomize 534 patients and have 454 (227 per group) patients complete the trial.

3.1.5 Analysis populations

The analysis populations are shown in **Table 3-1**. The modified intent-to-treat (mITT) population was defined in the Statistical Analysis Plan (SAP) as all consented and randomized patients who had valid baseline diary data for the run-in interval, had taken at least 1 dose of study medication, and had at least 1 day of on-treatment diary data. This definition of the mITT is standard in studies of this type, but might introduce bias because a patient starting study intervention might not start the diary as a result of the intervention received, which is counter to the intent-to-treat (ITT) principle. However, all patients in this study beginning study intervention initiated the diary and therefore this type of bias was precluded. The difference

between the all randomized and the mITT population was small as shown in the following table. The patients excluded to create the mITT population are not regarded as affecting the results of either study.

Table 3-1 Phase 3 analysis populations

	Study N30-003		Study N30-004	
	LDMP	**Placebo**	**LDMP**	**Placebo**
All randomized/ITT	306	308	285	285
mITT	301	305	284	284

ITT=intent-to-treat; mITT=modified intent-to-treat.

3.1.6 Handling of missing data

In general, the outcome data from the diary are computed as weekly measures and then rescaled to daily values in order to maintain compatibility with precedent work in VMS. There are two general classes of missing diary data in these studies:

(1) Daily diary entries can be missing. An imputation algorithm was used to "fill-in" missed daily entries in order to realize a weekly diary data measure. If the patient had entered fewer than 4 days of diary data in a 1-week treatment interval, then the average of the hot flash diary data over the most recent previous 7 days' entries was imputed.

(2) Insufficient daily diary data can be missing, thereby resulting in a patient having missing data for that week, or a patient can leave the study, thereby missing all subsequent weekly data.

Most of the analyses presented in this document use observed mITT data for the assessment time applicable to the analysis being done, a so-called completers analysis. A variety of methods were used to assess the impact of the missing data, and these analyses are described in Appendix D.

However, the amount of missing data is not regarded as being a major issue as detailed in Appendix D. For example, in Study N30-003, 89.9% and 87.7% of patients had Week 12 assessments, and in Study N30-004, 86.6% and 90.5% of patients had Week 12 assessments in the control and experimental arms, respectively. Alternative methods of analyses addressing the impact of missing data do not lead to different conclusions as seen in Appendix D.

3.1.7 Co-primary efficacy endpoints

In keeping with the FDA guidance document for trial design, each study included 4 co-primary endpoints: the median change in daily frequency of moderate to severe hot flashes from baseline to Week 4 and from baseline to Week 12, and the median change in daily severity of moderate to severe hot flashes from baseline to Week 4 and from baseline to Week 12. Study success was defined as meeting the statistical criterion for all four endpoints for that study, and therefore no type I error probability adjustment is necessary.

Daily hot flash frequency: The total number of moderate and severe hot flashes per day was calculated as the sum of moderate and severe hot flashes recorded in the daily hot flash diary each week divided by 7.

Daily hot flash severity score: The reduction in hot flash severity with treatment was determined using a severity score, computed from the diary data. The severity score used in the LDMP program is based on FDA requirements and precedent set by clinical studies of approved hormone therapies for the treatment of moderate to severe VMS. This severity score is computed for each patient for each day by weighting the sum of hot flashes by their relative severity and then dividing this numerator by the total number of hot flashes. Daily Severity Score = $[(2 \cdot F_m + 3 \cdot F_s)] / [(F_m + F_s)]$; F_m = frequency of moderate hot flashes and F_s = frequency of severe hot flashes.

The severity score can be calculated other ways (see Appendix E), such as using (i) mild, moderate and severe flashes to compute the daily weighted average (approved HT therapies for VMS indication), or (ii) the hot flash composite score $[(2 \cdot F_m + 3 \cdot F_s)]$ (Stearns et al 2000, Stearns et al 2003a, Stearns 2005).

The efficacy variables were measured at multiple time points during the Phase 3 studies. Since the prespecified normality criterion was not met, a two-group nonparametric test at each time point was used. This nonparametric test was a rank-transformed analysis of covariance (ANCOVA)/nonparametric method with baseline as the covariate

3.1.8 Prespecified supportive analyses

3.1.8.1 Clinical meaningfulness

The magnitude of the effect size of the frequency change primary endpoint can be referred to other outcomes in order to gain a broader understanding of the effect size observed for the primary endpoint. For example, the Patient Global Impression of Improvement (PGI-I) scale is a patient-reported outcome (PRO) that is widely accepted as reflecting a patient's improvement as a result of an intervention in clinical trials. In Study N30-003, where the PGI-I was implemented, a method based on the receiver operating characteristic (ROC) model was used to relate the frequency change effect size to the results from the PGI-I as an anchor. Patients were considered to be improved if their PGI-I score was less than or equal to 3 (3 = a little better; 2 = much better; 1= very much better). This PGI-I cut-off was used to classify patients into a dichotomy of "improved" versus "not improved." Using this dichotomy, the ROC analysis was used to derive an optimal cut-off for the frequency change primary endpoint and this frequency change cut-off was used to classify patients as responders versus nonresponders.

3.1.8.2 Persistence of benefit

A responder analysis of the persistence of benefit of LDMP versus placebo was conducted in Study N30-004. Responders were defined as patients who achieved a ≥50% reduction from baseline in frequency of moderate to severe hot flashes at Week 24. The percent change in hot

flash frequency was calculated using the formula: Percent reduction at Week 24 = [(F_m + F_s at baseline) – (F_m + F_s at Week 24) / F_m + F_s at baseline] × 100%; F_m = frequency of moderate hot flashes and F_s = frequency of severe hot flashes.

The logit model was used to analyze the proportion of responders with baseline number of hot flashes as a covariate in the model. Patients who withdrew before Week 24 and those who achieved <50% reduction from baseline were considered failures.

3.1.9 Secondary endpoints

Table 3-2 lists all the secondary endpoints analyzed in the Phase 3 studies. Forest plots for 5 clinically relevant outcomes and primary endpoints are found in Section 3.3.10, nighttime awakenings are discussed in Section 3.3.8, and results of secondary endpoints for each study are tabulated in Appendices F and G.

Table 3-2 Secondary endpoints analyzed in LDMP Phase 3 studies

1. Mean number of hot flashes per day.
2. Mean hot flash frequency for Weeks 1 through 12.
3. Mean hot flash severity for Weeks 1 through 12.
4. Change from baseline in total number of awakenings due to hot flashes per day (using sleep diary) (Appendix H).
5. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 4 for BMI <32 and ≥32 groups.
6. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to Week 12 for BMI <32 and ≥32 groups.
7. Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 4 for BMI <32 and ≥32 groups.
8. Mean change in severity of moderate to severe vasomotor symptoms from baseline to Week 12 for BMI <32 and ≥32 groups.
9. Change from baseline in climacteric symptoms at Week 12, using the Greene Climacteric Scale (GCS) (Appendix I).
10. Assessment of interference of hot flashes, using the Hot Flash Related Daily Interference Scale (HFRDIS) (Appendix J).
11. Number of responders, with responders defined as patients with a 50% reduction in hot flash frequency at the end of study.
12. Patient Satisfaction Questionnaire (PSQ): the number and percent of patients satisfied with the treatment will be assessed (Appendix K).
13. Proportion of patients with positive PGI-I Response: patients' overall improvement in VMS will be assessed using the PGI-I scale (Appendix L).
14. Proportion of patients with positive Clinical Global Impression (CGI) Response: patients' overall improvement in VMS from baseline will be assessed using the CGI scale (Appendix M).
15. Proportion of patients with positive Numerical Rating Scale (NRS) Response: patients' overall improvement in VMS from baseline will be assessed using the NRS (Appendix N).
16. Assessment of sexual functioning, using the Arizona Sexual Experience Scale (ASEX) (Appendix O).
17. Assessment of anxiety and depression, using the Hospital Anxiety and Depression Scale (HADS) (Appendix P).
18. Assessment of mood, using the Profile of Mood States (POMS) questionnaire (Appendix Q).
19. Assessment of the effect of LDMP compared with placebo on BMI.

3.2 Proof-of-concept Phase 2 study N30-002

The proof-of-concept Phase 2 study (N30-002) was an 8-week, multicenter, double-blind, randomized study of LDMP 7.5 mg versus placebo in patients with >7 to 8 moderate to severe hot flashes daily, or 50 to 60 weekly, for at least 30 days. In this study, LDMP was more effective than placebo as shown by larger decreases in the frequency and severity of moderate and severe hot flashes. These results established the proof of concept and provided information relevant to the Phase 3 study designs, including the estimation of effect size and the decision to extend the placebo run-in period for a longer duration. Appendix B provides a more detailed discussion of the N30-002 study design and results.

3.3 Phase 3 studies N30-003 and N30-004 – Results

Results of the pivotal Phase 3 N30-003 and N30-004 studies demonstrated the efficacy of LDMP for the treatment of moderate to severe VMS associated with menopause. Patients who received LDMP had a statistically significant reduction in hot flash frequency at Weeks 4 and 12 in both studies and in hot flash severity at Week 4 in both studies and Week 12 in the N30-004 study. In Study N30-003, the reduction in hot flash severity at Week 12 numerically favored LDMP; however, this one endpoint failed to meet statistical criterion. In study N30-003, more LDMP-treated patients reported feeling either “little better,” “much better,” or “very much better” on the PGI-I scale compared to placebo-treated patients, thereby demonstrating that the efficacy of LDMP was clinically meaningful to patients. (Additional efficacy topics including effect modification analyses [Section 3.3.6**]** and exploratory analyses to assess severity [Appendix E**]** are provided).

3.3.1 Patient disposition

Table 3-3 provides an overview of patient disposition in the Phase 3 program. In the 12-week N30-003 study, 614 patients were randomized across 70 US study sites, 306 in the LDMP group and 308 in the placebo group. A similar percentage of patients in both groups completed the study, 271/306 patients treated with LDMP (88.6%) and 278/308 with placebo (90.3%).

In the 24-week N30-004 study, 570 patients were randomized across 65 US study sites, 285 patients in each treatment group. More patients treated with LDMP (235/285 [82.5%]) than placebo (218/285 [76.5%]) completed the study.

Table 3-3 Patient disposition, mITT Population, Studies N30-003 and N30-004

	N30-003		N30-004	
	Placebo	**LDMP**	**Placebo**	**LDMP**
Randomized patients, n	308	306	285	285
mITT population, n (%)	305 (99.0)	301 (98.4)	284 (99.6)	284 (99.6)
Completed the trial, n (%)	278 (91.1)	271 (90.0)	218 (76.8)	235 (82.7)
Discontinued, n (%)	27 (8.9)	30 (10.0)	66 (23.2)	50 (17.6)
Reason for discontinuation, n (%)				
AE/SAE	4 (1.3)	7 (2.3)	15 (5.3)	15 (5.3)
At patient's request	12 (3.9)	8 (2.7)	34 (12.0)	15 (5.3)
Protocol-specified CSSRS/STS discontinuation criteria	1 (0.3)	1 (0.3)	1 (0.4)	4 (1.4)
Investigator's/sponsor's opinion, continuation in study would be detrimental to patient's well-being	1 (0.3)	2 (0.7)	2 (0.7)	0
Patient not able to comply with study requirements	2 (0.7)	1 (0.3)	4 (1.4)	1 (0.4)
Other	7 (2.3)	11 (3.7)	10 (3.5)	15 (5.3)

AE=adverse event; CSSRS=Columbia Suicide Severity Rating Scale; mITT=modified intent-to-treat; SAE=serious AE; STS= Suicidal Tracking Scale.

3.3.2 Patient demographic and baseline characteristics

The mITT population of Study N30-003 comprised 606 postmenopausal women, average age 54.7 years. Patients in both treatment groups had similar mean baseline VMS frequency, severity score, and number of nighttime awakenings (**Table 3-4**). The mITT population of Study N30-004 comprised 568 postmenopausal women, average age 54.4 years; baseline symptom parameters were similar in both treatment groups (**Table 3-4**).

The demographic and baseline characteristics were similar in the N30-003 and N30-004 studies, except N30-003 included higher percentages of Hispanic/Latino and Black patients compared with N30-004. In both studies, the baseline mean number of moderate to severe daily hot flashes exceeded the minimum number recommended (more than 7 moderate to severe hot flashes per day) in the FDA guidance (US FDA Draft Guidance, January 2003), confirming enrollment of the correct population of women.

Table 3-4 Demographics and baseline characteristics, mITT Population, N30-003 and N30-004

	N30-003		N30-004	
Statistic	**Placebo N=305**	**LDMP N=301**	**Placebo N=284**	**LDMP N=284**
Age (years)				
n	305	301	284	284
Mean (SD)	54.5 (6.27)	54.9 (5.95)	54.5 (5.74)	54.2 (5.47)
Median	53	54	54	54
Min, Max	40, 79	40, 73	40, 74	41, 70
Ethnicity, n (%)				
Hispanic/Latino	37 (12.1)	27 (9.0)	21 (7.4)	16 (5.6)
Not Hispanic/Latino	268 (87.9)	274 (91.0)	263 (92.6)	268 (94.4)
Race, n (%)				
All Other	7 (2.3)	2 (0.7)	0 (0.0)	4 (1.4)
American Indian/Alaska Native	1 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)
Asian	1 (0.3)	1 (0.3)	6 (2.1)	3 (1.1)
Black	93 (30.5)	106 (35.2)	53 (18.7)	69 (24.3)
European/Middle Eastern	1 (0.3)	0 (0.0)	1 (0.4)	2 (0.7)
Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
White/Caucasian	202 (66.2)	190 (63.1)	224 (78.9)	205 (72.2)
Body mass index (obesity)[a] (kg/m^2)				
n	305	300	284	284
Mean (SD)	29.68 (5.94)	29.25 (6.21)	28.33 (4.92)	27.95 (5.11)
Median	29.0	28.3	27.7	27.4
Min, Max	19.0, 56.5	16.8, 60.7	18.7, 39.7	18.3, 40.6
Weight (kg)				
n	305	301	284	284
Mean (SD)	79.5 (17.3)	78.5 (17.5)	75.7 (14.9)	75.8 (14.8)
Median	78.0	75.9	73.7	73.5
Min, Max	46.3, 153.8	37.6, 175.5	45.4, 124.7	48.6, 120.2
Menopause onset type, n (%)				
Natural onset	253 (83.0)	242 (80.4)	230 (81.0)	227 (79.9)
Surgical onset	52 (17.0)	59 (19.6)	54 (19.0)	57 (20.1)
Daily hot flash frequency				
n	305	301	284	284
Mean (SD)	11.65 (4.39)	11.79 (4.87)	10.90 (3.96)	10.83 (3.86)
Median (min, max)	10.4 (3.7-36.7)	10.4 (4.1-39.6)	9.6 (3.4-31.7)	9.9 (2.3-33.6)
Daily hot flash severity				
n	305	301	284	284
Mean (SD)	2.53 (0.31)	2.53 (0.30)	2.53 (0.32)	2.53 (0.30)
Median (min, max)	2.5 (2.0-3.0)	2.5 (2.0-3.0)	2.5 (2.0-3.0)	2.5 (2.0-3.0)

Statistic	N30-003 Placebo N=305	N30-003 LDMP N=301	N30-004 Placebo N=284	N30-004 LDMP N=284
Daily number of awakenings due to hot flashes				
n	301	301	279	281
Mean (SD)	3.72 (2.36)	3.55 (1.94)	3.56 (1.93)	3.58 (1.98)
Median (min, max)	3.3 (0.1-28.1)	3.3 (0.0-13.7)	3.3 (0.0-11.5)	3.3 (0.0-15.2)

[a]Body mass index at baseline (kg/m²)=weight prior to randomization (kg)/([height prior to randomization (cm)/100]²).
Max=maximum; Min=minimum; mITT=modified intent-to-treat; SD=standard deviation.

3.3.3 Co-primary endpoints: Daily frequency and severity at Week 4 and Week 12

The results for the co-primary endpoints are shown in **Table 3-5**. Reductions in the frequency of hot flashes relative to baseline met statistical criterion in patients treated with LDMP compared with placebo at both Weeks 4 and 12 in each Phase 3 study. The reduction in the severity of hot flashes was greater with LDMP compared with placebo, meeting the prespecified statistical criterion in Study N30-003 at Week 4, and in Study N30-004 at Week 4 and Week 12 (**Table 3-5**). For Study N30-003 the statistical criterion was not met at Week 12, but the effect favored the LDMP arm.

Table 3-5 Results for co-primary endpoints, mITT population, Studies N30-003 and N30-004

	Week 4			Week 12		
	Change from Baseline			Change from Baseline		
	Placebo	LDMP	P value	Placebo	LDMP	P value
Study N30-003: Co-primary endpoints						
Reduction in daily hot flash frequency (median), ranked ANCOVA	n = 293 -3.14	n = 289 -4.29	<0.0001	n = 274 -5.00	n = 264 -5.93	0.0090
Reduction in daily hot flash severity (median), ranked ANCOVA	n = 289 0.000	n = 281 -0.052	0.0017	n = 253 -0.018	n = 236 -0.058	0.1658
Study N30-004: Co-primary endpoints						
Reduction in daily hot flash frequency (median), ranked ANCOVA	n = 274 -2.500	n = 276 -3.786	<0.0001	n = 244 -3.857	n = 257 -5.571	0.0001
Reduction in daily hot flash severity (median), ranked ANCOVA	n = 271 -0.008	n = 268 -0.040	0.0368	n = 236 0.000	n = 245 -0.051	0.0064

Rank transformed analysis of covariance (ANCOVA), with baseline as a covariate in the model.

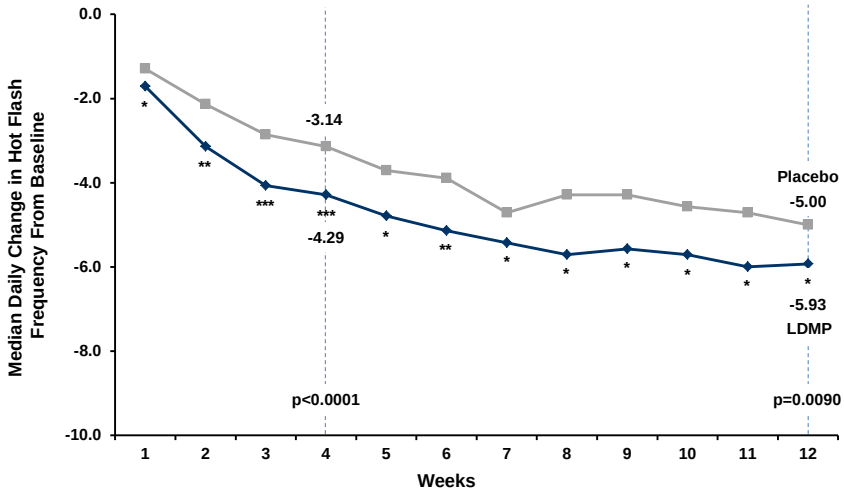
In Study N30-003, the daily median reduction in frequency of moderate to severe hot flashes in patients treated with LDMP versus placebo was 4.29 versus 3.14 at Week 4 ($p<0.0001$) and 5.93 versus 5.00 at Week 12 ($p=0.0090$), respectively (**Figure 3-2**). The daily median reduction in severity of moderate to severe hot flashes in patients treated with LDMP versus placebo, respectively, was 0.052 versus 0.000 at Week 4 ($p=0.0017$) and 0.058 versus 0.018 at Week 12 ($p=0.1658$) (**Figure 3-2**). Differences between the treatment groups were evident as early as the first week of treatment (**Figures 3-2** and **3-3**).

In Study N30-004, the daily median reduction in frequency of moderate to severe hot flashes in patients treated with LDMP versus placebo, respectively, was 3.786 versus 2.500 at Week 4 ($p<0.0001$) and 5.571 versus 3.857 at Week 12 ($p=0.0001$) (**Figure 3-3**). The daily median reduction in severity of moderate to severe hot flashes was 0.040 in patients treated with LDMP versus 0.008 with placebo at Week 4 ($p=0.0368$), and 0.051 versus 0.000 at Week 12, respectively ($p=0.0064$) (**Figure 3-3**).

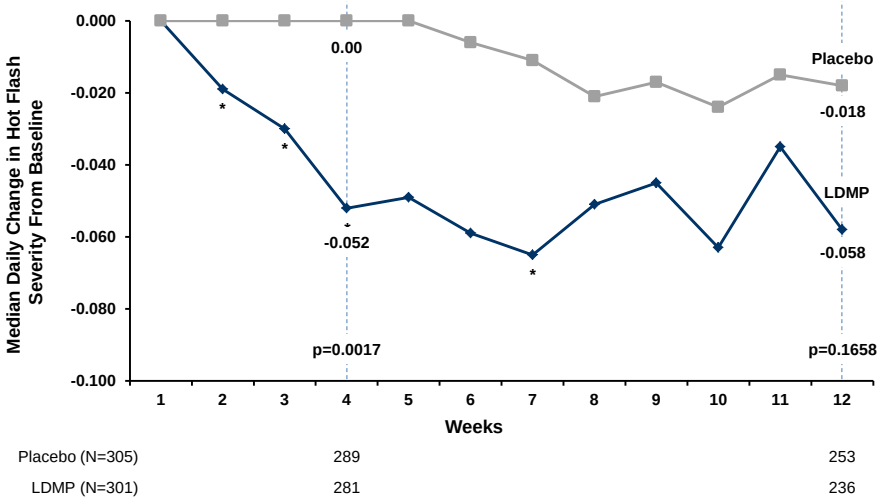
Results using the other ways of calculating the severity score such as using (i) mild, moderate and severe flashes to compute the daily weighted average (approved HT therapies for VMS indication), or (ii) the hot flash composite score $[(2 \cdot F_m + 3 \cdot F_s)]$ (Stearns et al 2000, Stearns et al 2003a, Stearns 2005) are discussed in Appendix E.

Figure 3-2 Median daily change in hot flash frequency and severity Week 1 through Week 12, mITT Population, Study N30-003

Frequency



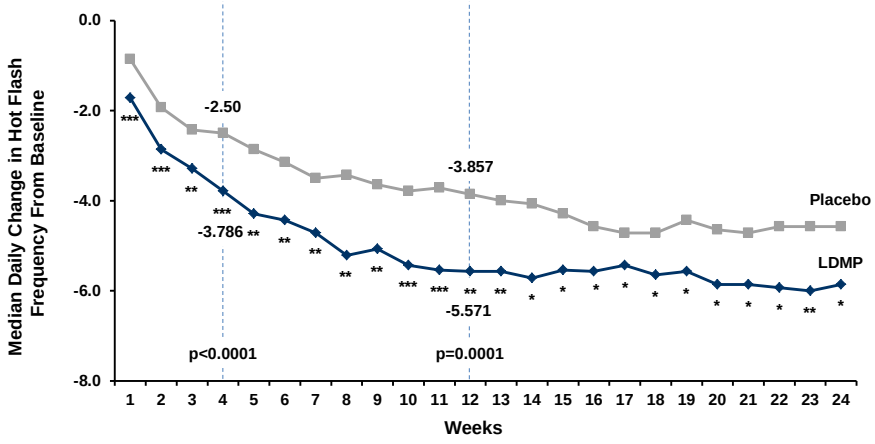
Severity



*p<0.05; **p<0.001; ***p<0.0001.
P values (based on median values) are results of rank transformed analysis of covariance (ANCOVA).
mITT=modified intent-to-treat.

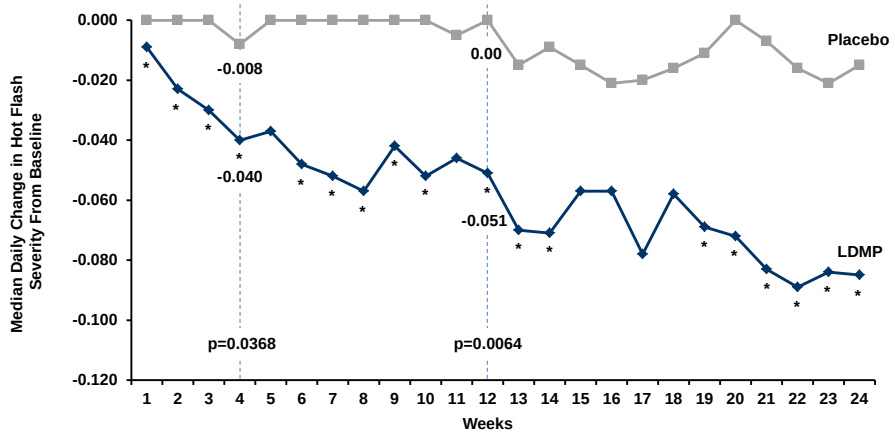
Figure 3-3 Median daily change in hot flash frequency and severity Week 1 through Week 12, mITT Population, Study N30-004

Frequency



Placebo (N=284)	274	244	215
LDMP (N=284)	276	257	234

Severity



Placebo (N=284)	271	236	201
LDMP (N=284)	268	245	213

*p<0.05; **p<0.001; ***p<0.0001.
P values (based on median values) are results of rank transformed analysis of covariance (ANCOVA).
mITT=modified intent-to-treat.

3.3.4 Co-primary endpoints using LOCF

The re-analysis of the primary endpoints using last observation carried forward (LOCF) presents an alternative view of the impact of missing data. The results for the co-primary endpoints using LOCF are shown in **Table 3-6** and are comparable to the results using ranked ANCOVA, as previously presented in **Table 3-5**.

Table 3-6 Co-primary endpoints using LOCF

	Week 4			Week 12		
	Change from Baseline			Change from Baseline		
	Placebo	LDMP	P value	Placebo	LDMP	P value
Study N30-003: Co-primary endpoints						
Reduction in daily hot flash frequency (median) using LOCF	n = 305 -3.14	n = 301 -4.29	<0.0001	n = 305 -5.00	n = 301 -5.86	0.0038
Reduction in daily hot flash severity (median) using LOCF	n = 305 0.000	n = 301 -0.047	0.0008	n = 305 -0.017	n = 301 -0.060	0.0728
Study N30-004: Co-primary endpoints						
Reduction in daily hot flash frequency (median) using LOCF	n = 284 -2.500	n = 284 -3.714	<0.0001	n = 284 -3.357	n = 284 -5.214	<0.0001
Reduction in daily hot flash severity (median) using LOCF	n = 284 -0.008	n = 284 -0.040	0.0084	n = 284 0.000	n = 284 -0.062	0.0020

3.3.5 Results of prespecified supportive endpoints

Prespecified supportive endpoints for the Phase 3 clinical development program included analysis of the clinical meaningfulness of the reduction in hot flashes anchored to patient-reported improvement in Study N30-003, and assessment of the persistence of benefit according to response at Week 24 in Study N30-004.

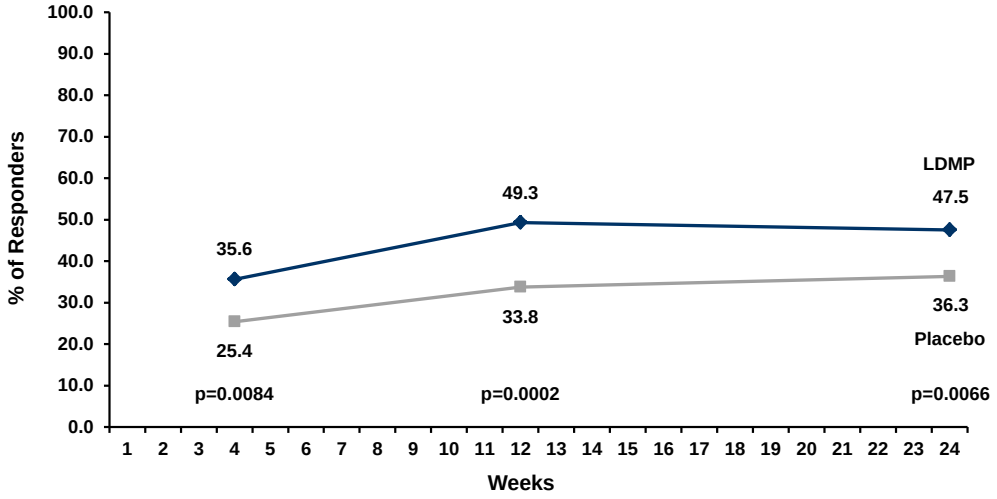
3.3.5.1 Clinical meaningfulness anchored to patient-reported improvement

The previously defined ROC analysis used to estimate the frequency change cutoff found significantly more responders in the LDMP group compared with the placebo group at Week 4 (58.5% LDMP, 47.2% placebo; p=0.0058). At Week 12, 47.8% of LDMP-treated patients were responders, compared with 41.6% of those receiving placebo (p=0.1332). Thus, this ROC analysis relating the PGI-I to the frequency change primary outcome demonstrates directional favorability for the LDMP arm based on the derived cut-off values.

3.3.5.2 Persistence of benefit over time

The persistence of benefit of LDMP extended to Week 24 in Study N30-004. In the N30-004 mITT population, more patients treated with LDMP (47.5%) than placebo (36.3%; p=0.0066) achieved a ≥50% reduction from baseline in frequency of moderate to severe hot flashes (defined as responders) at Week 24 (**Figure 3-4**). In this analysis, patients with missing data were treated as nonresponders.

Figure 3-4 Persistence of benefit at Week 24, mITT Population, Study N30-004

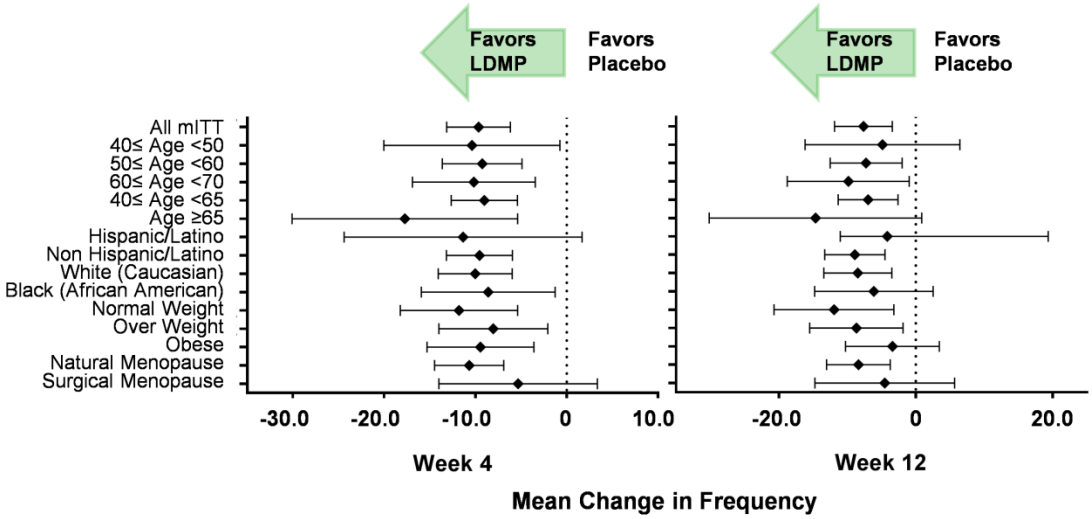


Responders: patients who achieved a ≥50% reduction.
P values are results of logistic model with baseline as a covariate in the model.
mITT=modified intent-to-treat.

3.3.6 Effect modification analyses

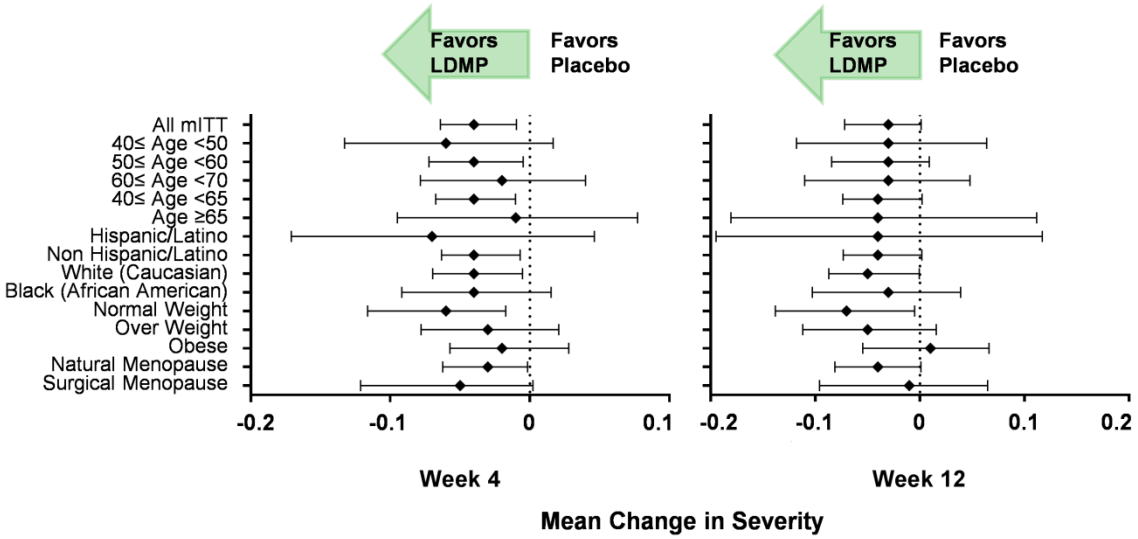
Effect modification analyses for the co-primary endpoints and the persistence of benefit analysis were conducted for the baseline attribute factors of age, race, ethnicity, BMI, and type of menopause onset, and the results are shown in **Figures 3-5** through **3-7**. These results support the consistency of LDMP effect across the analyzed baseline attributes.

Figure 3-5 Effect modification analyses of mean frequency change (95% CI) in moderate to severe hot flashes at Week 4 and Week 12, mITT Population, Pooled Phase 3 Studies



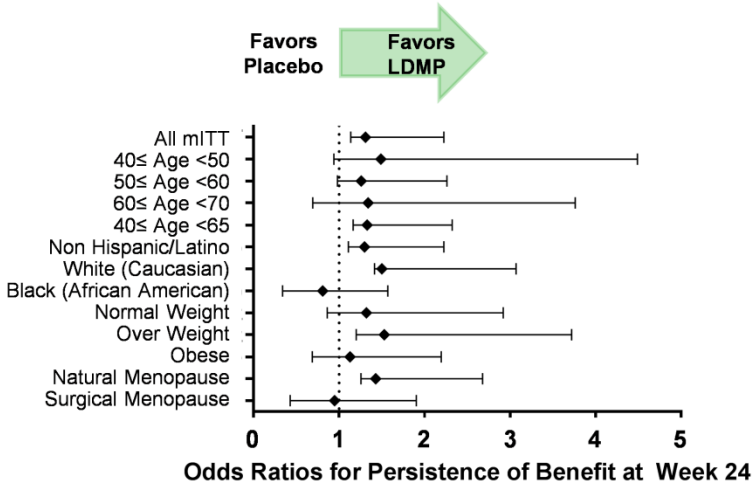
CI=confidence intervals; mITT=modified intent-to-treat.

Figure 3-6 Effect modification analyses of mean severity change (95% CI) in moderate to severe hot flashes at Week 4 and Week 12, mITT Population, Pooled Phase 3 Studies



CI=confidence intervals; mITT=modified intent-to-treat.

Figure 3-7 Effect modification analyses for persistence of benefit odds ratio (95% CI), mITT Population, Study N30-004



CI=confidence intervals; mITT=modified intent-to-treat.

3.3.7 PGI-I analysis

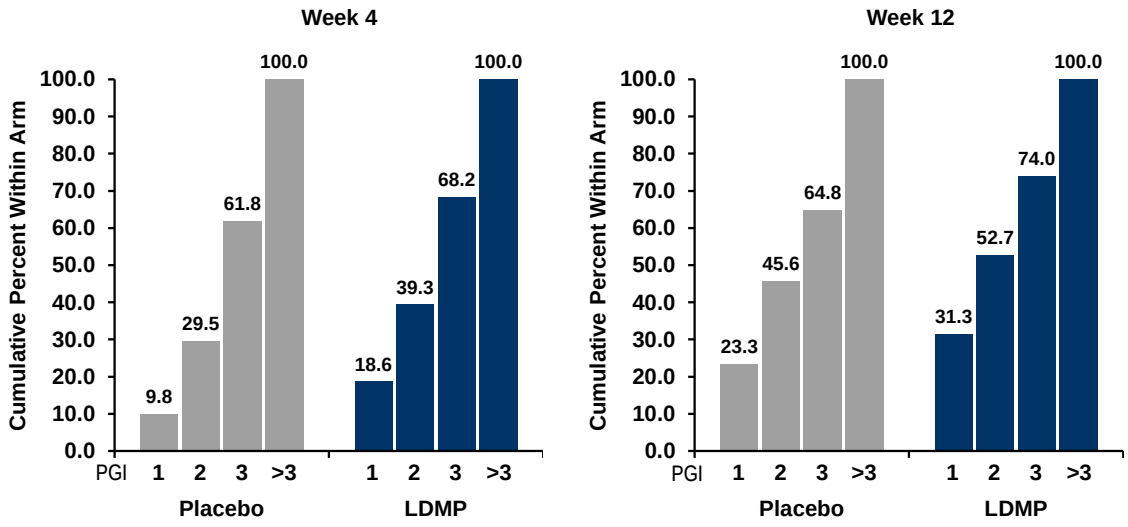
The PGI-I outcome is a PRO on an ordinal categorical scale. The PGI-I was assessed at Weeks 4 and 12 in Study N30-003, and was recorded as a score from 1 to 7 where 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very

much worse. Few patients in either treatment group reported scores >3 at Week 4 (13 of 285 patients treated with LDMP and 4 of 280 with placebo) or Week 12 (11 of 291 with LDMP and 15 of 287 with placebo). Therefore, the analyses of PGI-I were performed for the 4-level indications of 1, 2, 3, and >3.

At Week 4 and Week 12, PGI-I was analyzed as an ordinal categorical and as an analysis of response (≤3 and ≥4). The amount of missing data for PGI-I was similar to the missing data in the primary endpoints with no evidence of a notable between-arm difference in missing data. The analysis of PGI-I used observed data.

Figure 3-8 shows the outcome for the PGI-I analysis at Week 4 and Week 12 (cumulative distribution). Within each week, a distinct shift to the left (towards more improved categories) was evident in the LDMP group as compared with placebo; specifically, there was a higher cumulative percentage of patients in the LDMP group compared with the placebo group for each week and at scores of 1, 2, and 3.

Figure 3-8 PGI-I cumulative distribution by treatment group at Week 4 and Week 12, mITT Population, Study N30-003



mITT=modified intent-to-treat ; PGI-I=Patient Global Impression of Improvement.

An exact between-arm test for PGI-I can be performed by the exact Wilcoxon test. Ordinal categorical data can also be analyzed using the proportional-odds cumulative logit model. The advantage of the exact Wilcoxon test is its exactness whereas the advantage of the proportional-odds cumulative logit model is that the effect size can be estimated. **Table 3-7** presents the results of these between-arm tests. Notably, the p values from the two methods are quite similar.

Table 3-7 PGI-I between-arm tests using exact Wilcoxon and proportional-odds cumulative logit models

Week	Exact Wilcoxon p-value	Proportional-odds cumulative logit	Proportional-odds cumulative logit effect size estimate (95% CI)
4	0.0086	0.0086	1.495 (1.108 to 2.017)
12	0.0164	0.0162	1.455 (1.071 to 1.976)

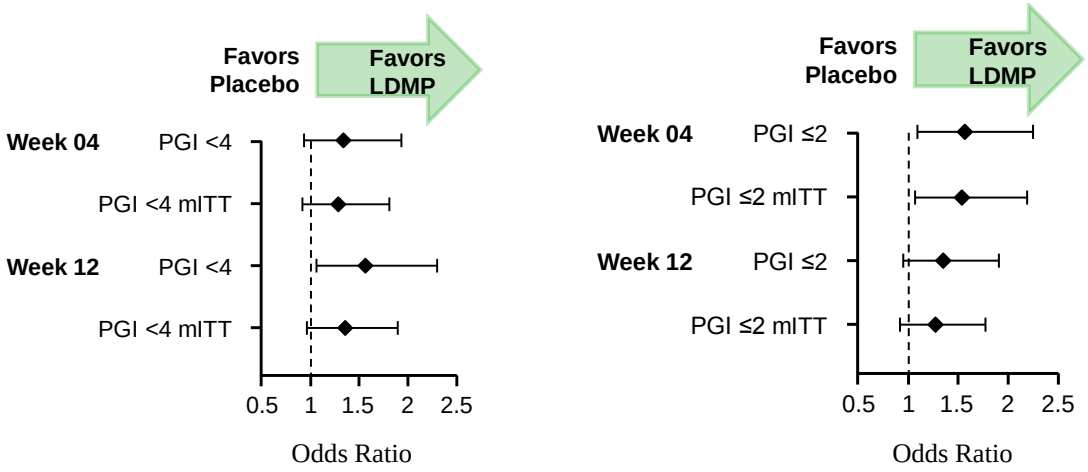
CI=confidence interval; PGI-I=Patient Global Impression of Improvement.

The proportional-odds cumulative logit effect size estimate is the odds[1] of the experimental arm (LDMP) having a lower score category (more improvement) divided by the odds of the control arm (placebo) having a lower score category (more improvement). A number greater than 1 means the LDMP arm has more improvement relative to the placebo arm. For example, at Week 4, the odds of a lower category of PGI-I score in the LDMP group is approximately 1.5 times the same odds for the placebo group. The cumulative logit model had no lack of fit, consistent with there being a general shift toward lower categories in the LDMP arm.

PGI-I response is defined as a score of ≤3 (ie, <4) at a particular week. The measure of effect is the odds ratio, ie, the odds of response in the LDMP arm divided by the odds of response in the placebo arm. An odds ratio estimate of >1 favors the LDMP arm**. Figure 3-9** illustrates these analyses, and shows consistency of effect size across all analyses. The analysis of PGI-I provides further evidence that LDMP is superior to placebo at both Week 4 and Week 12.

[1] The odds ratio is defined as follows: The probability of being in a lower category divided by the probability of being in a higher category. An odds of 1 means no difference in these probabilities whereas an odds >1 favors the lower category and conversely. For these data the odds are generally <1 from category-to-category. However, the ratio of the odds in the experimental arm divided by the odds in the control arm (odds ratio) favors the experimental arm (between-arm estimated odds ratio is >1). The model is consistent with this odds ratio being the same from category-to-category and that this single estimated odds ratio is meaningfully >1 for both weeks (95% confidence intervals on the estimated odds ratios exclude one).

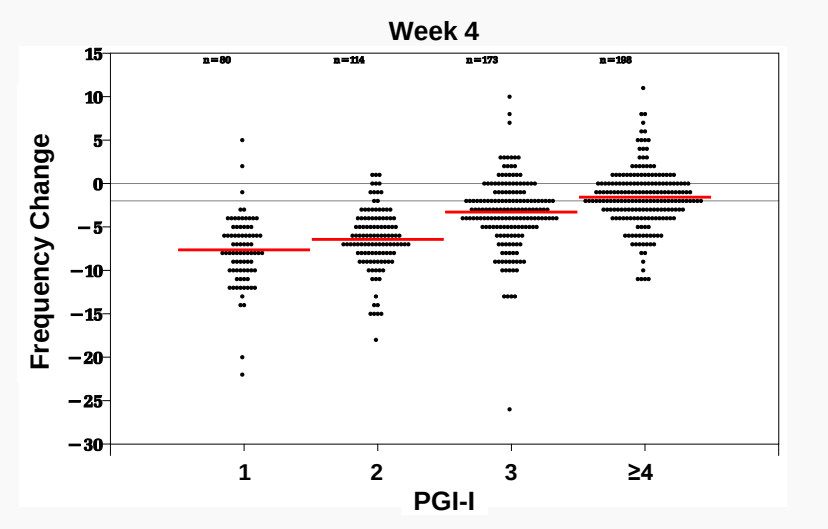
Figure 3-9 PGI-I response analyses at Week 4 and Week 12, Study N30-003

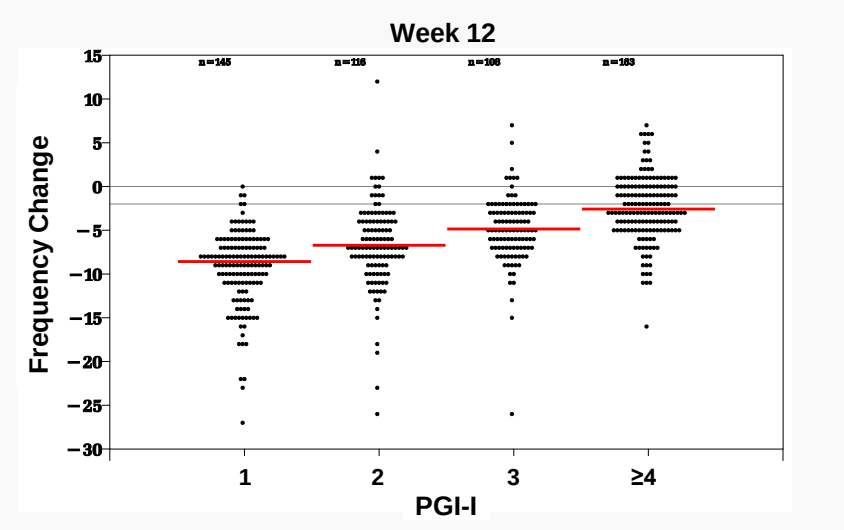


mITT=modified intent-to-treat ; PGI-I=Patient Global Impression of Improvement.

In addition, PGI-I is correlated with the primary endpoint of the reduction in frequency of hot flashes in the N30-003 study. This correlation is shown in **Figure 3-10** for Study N30-003 at both Weeks 4 and 12. The strength of this association provides evidence that the change in frequency is meaningful. In particular, note that a difference from PGI-I category ≥4 to 1 is associated with a decrease of approximately 7 daily moderate or severe hot flashes.

Figure 3-10 Correlation between hot flash frequency and PGI-I score Week 4 and Week 12, mITT Population, N30-003





mITT=modified intent-to-treat; PGI-I=Patient Global Impression of Improvement.
Red lines represent median; reference lines corresponds to change of 0 and -2 per day.

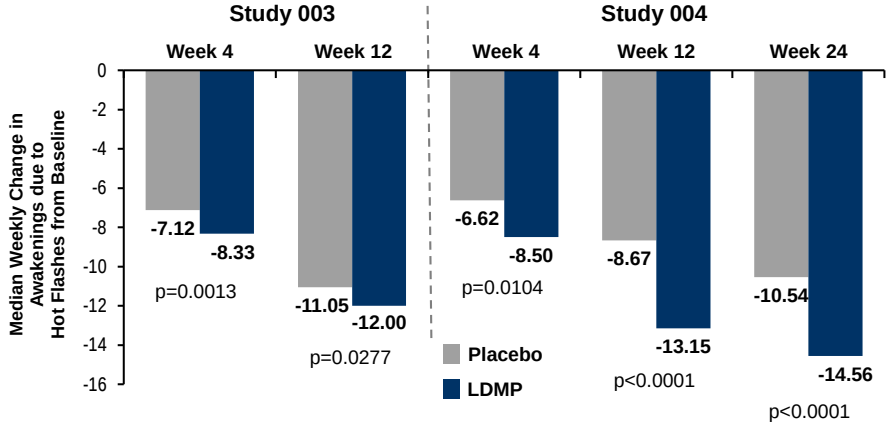
3.3.8 Nighttime awakenings analysis

Treatment with LDMP significantly reduced the number of nighttime awakenings due to hot flashes compared with placebo in the mITT populations of both Phase 3 studies.

In both Phase 3 studies, the median weekly number of nighttime awakenings due to moderate to severe hot flashes at baseline was similar in the LDMP and placebo groups: 23.15 and 23.15, respectively, with LDMP and placebo in Study N30-003; and 22.75 and 22.91, respectively, in Study N30-004. The median reduction from baseline in the number of nighttime awakenings due to moderate to severe hot flashes was significantly greater with LDMP than with placebo at both

Week 4 and Week 12 in Studies N30-003 and N30-004 and at Week 24 in Study N30-004 (**Figure 3-11**).

Figure 3-11 Median weekly change in number of nighttime awakenings due to hot flashes, mITT Population, N30-003 and N30-004



P values are results of rank transformed analysis of covariance (ANCOVA).
mITT=modified intent-to-treat.

3.3.9 Frequency change response of ≥2 per day

In the mITT populations of the Phase 3 studies, significantly more patients treated with LDMP than placebo achieved a ≥2 per day reduction from baseline in frequency of moderate to severe hot flashes at Weeks 4 and 12 (**Table 3-8**).

Table 3-8 Proportion of patients achieving a ≥2 per day reduction in frequency of moderate to severe hot flashes, mITT Population, N30-003 and N30-004

	N30-003			N30-004		
Statistic	**Placebo n (%)**	**LDMP n (%)**	**P value[a]**	**Placebo n (%)**	**LDMP n (%)**	**P value[a]**
Week 4						
Total observed	305	301		284	284	
≥2 per day	175 (57.38)	215 (71.43)	0.0003	156 (54.93)	188 (66.20)	0.0061
<2 per day	130 (42.62)	86 (28.57)		128 (45.07)	96 (33.80)	
Week 12						
Total observed	305	301		284	284	
≥2 per day	208 (68.20)	228 (75.75)	0.0390	168 (59.15)	198 (69.72)	0.0087
<2 per day	97 (31.80)	73 (24.25)		116 (40.85)	86 (30.28)	

[a]P values from logit model.
mITT= modified intent-to-treat.

3.3.10 Consistency of LDMP effect across multiple outcomes

Consistency of direction and magnitude of effect across multiple outcomes provides consensus evidence of the effect of LDMP. A broader picture of the nature of effect is supported when these outcomes are meaningful and measure different aspects of outcome. To illustrate the general effect direction across multiple outcomes, each outcome must be converted to the compatible scales. One simple and readily accessible method is to assure that each outcome is converted to a response dichotomy. **Table 3-9** shows the outcomes featured in this multiple outcome overview and the dichotomization and response criterion.

Table 3-9 Selected outcomes and response dichotomy

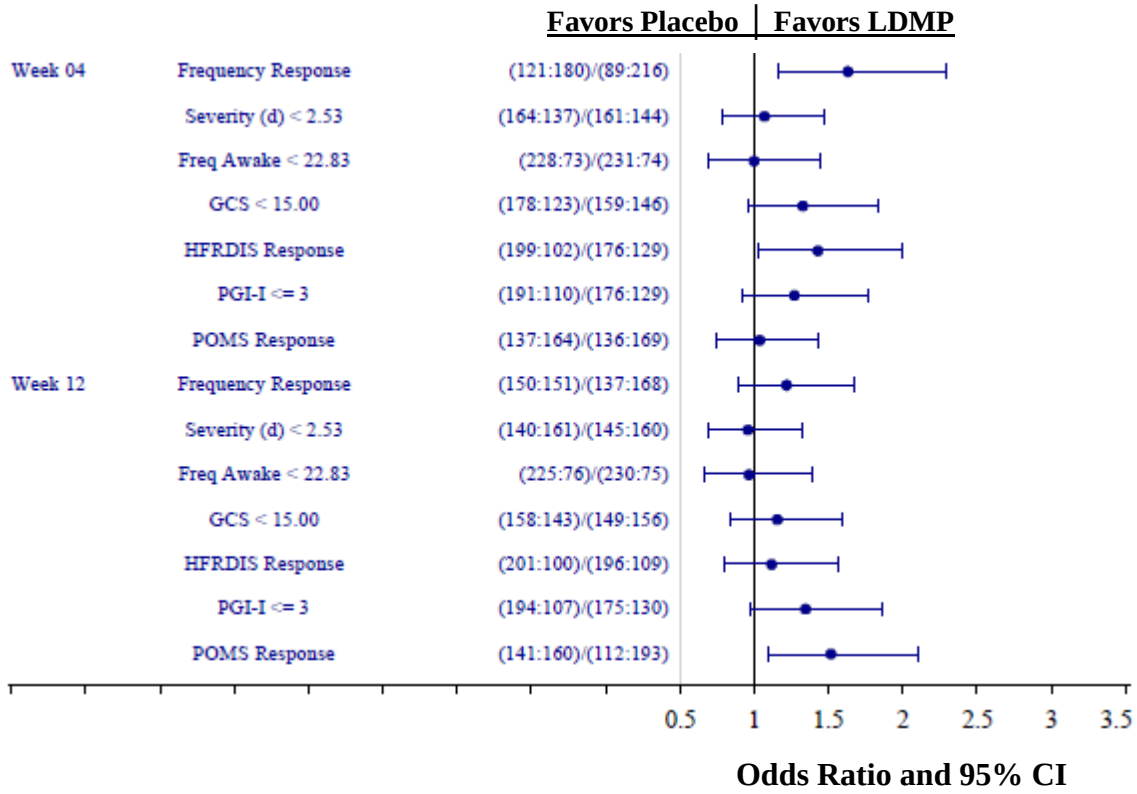
Measure	Source of dichotomization of outcome	Response criterion
Frequency of moderate or severe hot flashes	Pre-defined	More than 50% reduction compared with baseline
Severity score	Defined by data	Follow-up value below pooled baseline median
Frequency of nighttime awakenings	Defined by data	Follow-up value below pooled baseline median
GCS	Defined by data	Follow-up value below pooled baseline median
HFRDIS	Predefined	Change at follow-up is negative
PGI-I	Predefined	Follow-up level is 3 or less
POMS	Predefined	Change at follow-up is negative

GCS=Greene Climacteric Scale; HFRDIS=Hot Flash-Related Daily Interference Scale; PGI=Patient Global Impression of Improvement; POMS=Profile of Mood States.

Forest plots of the outcomes for each of these endpoints by study and week are shown in **Figures 3-12** and **3-13** with missing data changed to 'no response," therefore, these analyses are based on the full mITT population. These analyses were done using dichotomy with exact methods. For each analysis, the odds ratio estimate and the exact 95% confidence interval was computed. The frequencies associated with each analysis are shown on the graphs; the LDMP arm frequency odds are shown in the numerator and the placebo arm frequency odds are shown in the denominator. (Note that these exploratory analyses did not have applicable predefined statistical criteria and the study size was not planned based on these analyses.)

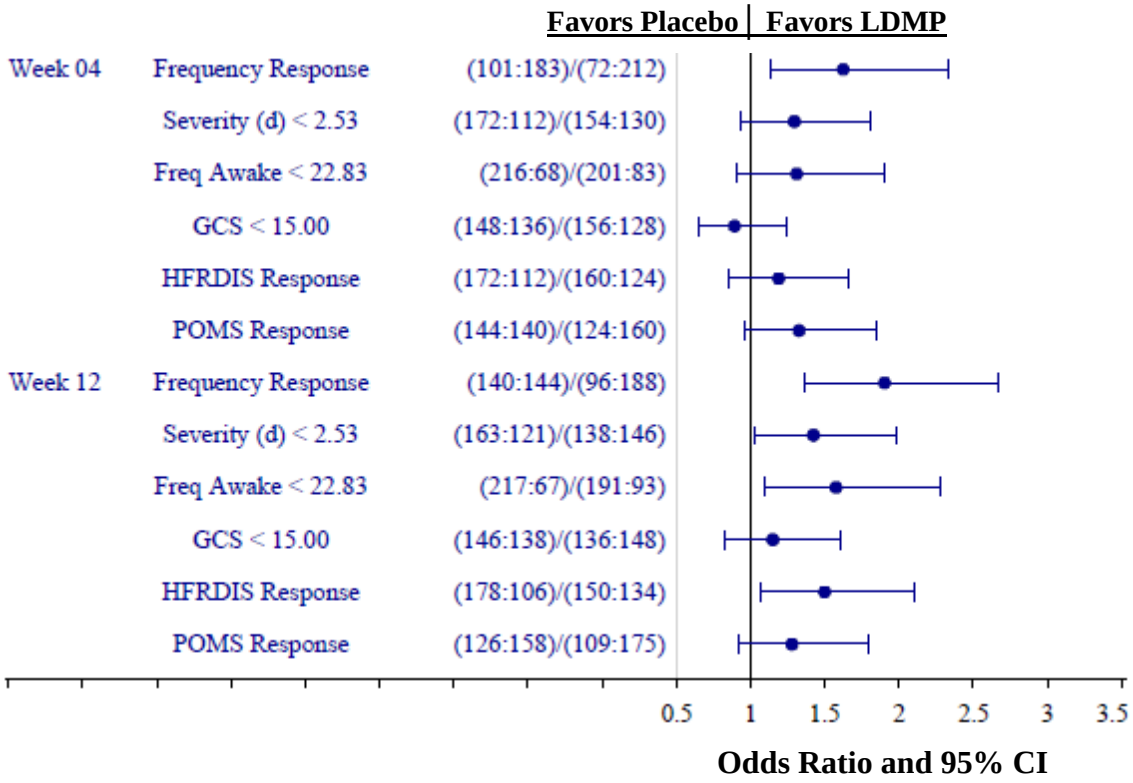
The general consistency across the outcomes and the information conveyed by the confidence intervals show that the hot flash reduction in the mITT population is generally supported by benefit with LDMP treatment in these other outcomes.

Figure 3-12 Multiple outcomes by treatment arm at Weeks 4 and 12, mITT Population, Study N30-003



CI=confidence interval; Freq Awake=frequency of nighttime awakenings; Freq response= hot flash frequency reduction; GCS= Greene Climacteric Scale; HFRDIS=Hot Flash-Related Daily Interference Scale; mITT=modified intent-to-treat; PGI=Patient Global Impression of Improvement; POMS=Profile of Mood States; Severity=severity score.

Figure 3-13 Multiple outcomes by treatment arm at Weeks 4 and 12, mITT Population, Study N30-004



CI=confidence interval; Freq Awake=frequency of nighttime awakenings; Freq response= hot flash frequency reduction; GCS= Greene Climacteric Scale; HFRDIS=Hot Flash-Related Daily Interference Scale; mITT=modified intent-to-treat; PGI=Patient Global Impression of Improvement; POMS=Profile of Mood States; Severity=severity score.

3.4 Efficacy Summary

The randomized, double-blind, placebo-controlled Phase 3 studies (N30-003 and N30-004) have demonstrated the efficacy of LDMP for the treatment of moderate to severe VMS associated with menopause.

Clinical meaningfulness of the effects of LDMP treatment on moderate to severe VMS was further evaluated through investigations of the relationship of frequency change to the additional endpoints. The directionality of these associations generally favors LDMP. In the N30-004 study, the persistence of benefit of LDMP treatment extended to 24 weeks.

The results of the effect modification analyses for the co-primary endpoints and persistence of benefit further support the effectiveness of LDMP across age categories, race, ethnicity, BMI, and type of menopausal onset.

Taken together, these studies provide substantial evidence for the efficacy of LDMP for the treatment of moderate to severe VMS associated with menopause.

4 SAFETY

In the clinical development program, LDMP 7.5 mg once daily demonstrated tolerability and a favorable safety in the population of patients treated for moderate to severe VMS associated with menopause. Paroxetine has been an approved drug since 1992 and has more than 20 years of real-world experience. Paroxetine has an established safety profile in psychiatric indications at doses from 10 to 60 mg. Paroxetine at currently available doses is already used to treat depression in this age group, including postmenopausal women who may also have VMS. It is also used off-label at higher doses than 7.5 mg to treat VMS in women who are not depressed.

LDMP was developed under Section 505(b)(2), and therefore relies on FDA's findings of safety for higher doses of paroxetine. No new or unexpected safety findings were observed in the clinical development program out to Week 24 with the 7.5 mg dose. The proposed label for LDMP 7.5 mg adopts the warnings, precautions, and drug-drug interactions that are described in the USPIs for paroxetine at higher doses.

Adverse events of special interest include those listed as warnings and precautions in the current labeling for higher-dose paroxetine (Paxil PI, Pexeva PI). These include suicidality, gastrointestinal (GI) or any other bleeding events, and fractures. Weight gain and sexual dysfunction are other adverse events associated with higher paroxetine doses and would be of particular concern in the postmenopausal population. These effects as well as discontinuation symptoms and other events known to be associated with SSRIs and SNRIs were evaluated.

In addition to the collection of adverse event data, suicidality, sexual dysfunction, and discontinuation symptoms were prospectively assessed using validated scales.

A total of 1276 patients who participated in the Phase 2 (N30-002) and Phase 3(N30-004 and N30-004) studies of LDMP comprise the primary pool for this safety analysis (All Controlled Studies Pool).

4.1 Methods

4.1.1 Evaluation of adverse events, laboratory values, vital signs, and electrocardiograms

AE data were collected throughout the studies and up to 7 days postdose, or up to 30 days postdose for AEs ongoing at the end of study and serious adverse events (SAEs). Coding of AEs was based on Medical Dictionary for Regulatory Activities (MedDRA) version 13.1. AEs that started or worsened after the first dose were considered treatment-emergent AEs.

Laboratory values were collected at screening and at the end of each study. Values of grade 3 or higher by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 were considered clinically significant. Vital signs and body weight were collected at baseline and Weeks 2, 4, and 12 (N30-003), and 24 (N30-004) in the Phase 3 studies, and at baseline and Weeks 1, 4, and 8 in the Phase 2 N30-002 study. Electrocardiograms (ECGs) were performed at screening and at the end of each study.

All safety summaries are descriptive; no inferential statistics were planned. Missing values were recorded as missing, were not imputed, and were excluded from the analyses of change from baseline.

4.1.2 Evaluation of suicidality

Suicidality was prospectively evaluated in the LDMP clinical development program, based on treatment-emergent AEs as well as data from suicidality scales.

In the first 2 studies (Phase 2 N30-002 and Phase 3 N30-004 studies), the Suicidality Tracking Scale (STS) (Appendix R), a prospective rating scale completed by patients, was used to assess suicidal ideation and behaviors (Coric et al 2009). Each of 8 STS items is scored on a 5-point Likert scale (0 = not at all, 1 = a little, 2 = moderately, 3 = markedly, and 4 = extremely).

Following initiation of these 2 studies, FDA issued guidance (US FDA Guidance for Industry, September 2010) recommending use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA) such as the Columbia-Suicide Severity Rating Scale (C-SSRS). Thus, the C-SSRS (Appendix S) was used in the next Phase 3 study (N30-003) and the Phase 1 PK study (N30-005). The C-SSRS is a prospective, semistructured, clinician-administered questionnaire. To pool the suicidality data for analysis, the STS scores were mapped to the C-SSRS domains of suicidal ideation and suicidal behavior using the C-CASA.

4.1.3 Evaluation of sexual dysfunction

Sexual dysfunction was evaluated based on treatment-emergent AEs, and with the Arizona Sexual Experience (ASEX) scale, a 5-item rating scale that quantifies sex drive, arousal, lubrication (women), ease of reaching orgasm, and orgasm satisfaction. Each item is rated on a 6-point scale (6 being worst) and the 5 scores are added for a possible total score ranging from 5 to 30. Patients with a total score ≥19, or a score ≥5 on any individual item, or a score ≥4 on any 3 items were considered to have sexual dysfunction. Patients completed the ASEX questionnaire at baseline and Weeks 4 and 12 (N30-003), and Week 24 (N30-004) in the Phase 3 studies and at baseline and Weeks 4 and 8 the Phase 2 N30-002 study.

4.1.4 Discontinuation-emergent signs and symptoms

Discontinuation-emergent signs and symptoms (DESS) were evaluated 7 days after the last dose using the DESS checklist, which is a 27-item, clinician-rated instrument that queries for signs and symptoms associated with SSRI treatment discontinuation or interruption (Appendix T) (Rosenbaum et al 1998). Patients are asked, “During the past 7 days, have you experienced any changes in the following symptoms?” Symptoms are categorized using a 5-point scale: Symptom not present, old symptom but unchanged, old symptom but improved, old symptom but worse, and new symptom.

4.2 LDMP safety population

A total of 1300 patients were evaluated in the LDMP clinical program; 659 received LDMP and 641 received placebo. The primary pool for the safety evaluation is the All Controlled Studies Pool (n=1276), which includes 635 patients treated with LDMP and 641 with placebo in the double-blind, placebo-controlled Phase 3 (N30-003 and N30-004) and Phase 2 (N30-002) studies (**Table 4-1**). These patients all received at least 1 dose of study drug and had at least 1 postdose safety assessment. Findings in the Phase 3 Studies Pool were generally similar to those of the All Controlled Studies Pool and results are described when relevant. The Phase 1 PK study (N30-005) was not integrated in this pool because it had a different study population (healthy postmenopausal women), no comparator treatment, and was not blinded.

Table 4-1 Patients receiving study drug by study and pool

Phase	Study or Pool	Placebo	LDMP	Total
3	N30-003	305	301	606
	N30-004	284	285	569
	Phase 3 Studies Pool	**589**	**586**	**1175**
2	N30-002	52	49	101
	All Controlled Studies Pool	**641**	**635**	**1276**
1	N30-005	NA	24	24
	Total	**641**	**659**	**1300**

NA=not applicable.

4.3 Patient disposition

Among 1276 patients in the All Controlled Studies pool, similar proportions of patients treated with LDMP (86.8%) and placebo (85.3%) completed the study (**Table 4-2**). The most common reasons for discontinuation in both treatment groups were AE/SAE (3.8%, 3.1%), patient request (3.9%, 7.2%), and lost to follow-up (2.2%, 1.1%). Four patients treated with LDMP and 2 with placebo discontinued due to their responses on the C-SSRS or STS.

Table 4-2 Patient disposition, All Controlled Studies Pool, Safety Population

Parameter	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Completed the study	547 (85.3)	551 (86.8)
Discontinued	94 (14.7)	84 (13.2)
Reason for discontinuation		
AE/SAE	20 (3.1)	24 (3.8)
At their own request	46 (7.2)	25 (3.9)
C-SSRS/STS	2 (0.3)	4 (0.6)
In the Investigator's or Sponsor's opinion, continuation in the study would be detrimental to the patient's well-being	3 (0.5)	2 (0.3)
The patient is not able to comply with the study requirements	6 (0.9)	2 (0.3)
Other: Not specified	1 (0.2)	0
Other: Elective surgery	0	1 (0.2)
Other: Eligibility criteria not met	4 (0.6)	3 (0.5)
Other: Lack of efficacy	2 (0.3)	2 (0.3)
Other: Lost to follow-up	7 (1.1)	14 (2.2)
Other: Noncompliance	1 (0.2)	2 (0.3)
Other: Relocation	1 (0.2)	2 (0.3)
Other: Withdrew consent	1 (0.2)	3 (0.5)

AE=adverse event; C-SSRS=Columbia Suicide Severity Rating Scale; SAE=serious adverse event; STS=Suicidality Tracking Scale.

4.4 Patient demographics

Demographic characteristics were balanced between the LDMP and placebo treatment groups in the All Controlled Studies pool (**Table 4-3**). The mean age of these postmenopausal women was 54.7 years in those treated with LDMP and 54.5 years with placebo. The majority of patients were Caucasian or Black and not of Hispanic/Latino ethnicity.

Table 4-3 Demographics, All Controlled Studies Pool

Characteristic	Statistic/Category	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Age (years)	n	641	635
	Mean	54.5	54.7
	SD	5.96	5.72
	Median	54	54
	Minimum, Maximum	40, 79	40, 73
Age category (years), n (%)[a]	≥40 to <50	121 (18.9)	103 (16.2)
	≥50 to <60	407 (63.5)	413 (65.0)
	≥60 to <70	104 (16.2)	111 (17.5)
	≥70	9 (1.4)	8 (1.3)
Ethnicity, n (%)	Hispanic/Latino	59 (9.2)	44 (6.9)
	Not Hispanic/Latino	582 (90.8)	591 (93.1)
Race, n (%)	American Indian/Alaska Native	1 (0.2)	2 (0.3)
	Asian	8 (1.2)	4 (0.6)
	Black	161 (25.1)	190 (29.9)
	European/Middle Eastern	2 (0.3)	2 (0.3)
	Native Hawaiian/Pacific Islander	0 (0.0)	1 (0.2)
	Other	7 (1.1)	6 (0.9)
	White/Caucasian	462 (72.1)	430 (67.7)

[a]Studies excluded patients aged <40 years.
SD=standard deviation.

4.5 Baseline disease characteristics

Medical conditions identified for evaluation based on the known safety profile of paroxetine and other SSRIs and SNRIs included cardiovascular conditions, hepatic conditions, and GI or other bleeding conditions. At baseline in the All-Controlled Studies Pool, similar proportions of patients in the LDMP and placebo groups had these conditions (**Table 4-4**). Mean BMI and body weight were similar across treatment groups. Approximately 70% of patients in both groups were overweight or obese.

Table 4-4 Baseline disease characteristics, All Controlled Studies Pool

Baseline Characteristic	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with cardiovascular conditions, n (%)	193 (30.1)	211 (33.2)
Patients with hepatic conditions, n (%)	6 (0.9)	10 (1.6)
Patients with bleeding or GI conditions, n (%)	9 (1.4)	10 (1.6)
Body mass index (kg/m²)		
n	640	634
Mean	28.8	28.5
SD	5.57	5.74
Median	28.1	27.8
Minimum, Maximum	18.7, 56.2	16.2, 60.9
Body mass index category, n (%)		
Underweight (<18.5 kg/m²)	0 (0.0)	3 (0.5)
Normal (≥18.5 and <25.0 kg/m²)	180 (28.1)	191 (30.1)
Overweight (≥25.0 and <30.0 kg/m²)	211 (32.9)	223 (35.1)
Obese (≥30.0 kg/m²)	249 (38.8)	217 (34.2)
Weight (lb)		
n	640	635
Mean	170.1	169.5
SD	36.0	35.8
Median	166.2	163.1
Minimum, Maximum	95.5, 338.0	80.0, 389.0

GI=gastrointestinal; SD=standard deviation.

4.6 Overall exposure

In the All Controlled Studies Pool, there were no important differences in overall exposure or in exposure by duration category between treatment groups. Most patients received study drug for more than 4 weeks, and the majority for more than 12 weeks. A total of 235 patients treated with LDMP (218 with placebo) completed 24 weeks of treatment in study N30-004 (**Table 4-5**).

Study drug compliance was achieved in 88.2% of patients treated with LDMP and 86.6% with placebo.

Table 4-5 Overall exposure (days), All Controlled Studies Pool

Descriptive statistic (days)	Placebo N=641	LDMP 7.5 mg N=635
n	633	622
Mean	107.6	110.9
SD	48.3	48.8
Median	85.0	85.0
Min	2	2
Max	177	180

Duration of exposure=study drug stop date – randomization date (first dose date was not captured); n value includes only patients who received at least one dose of study medication and had at least one post-dose safety assessment.
SD=standard deviation.

4.7 Serious adverse events

In the All Controlled Studies Pool, 14 (2.2%) patients treated with LDMP and 9 (1.4%) with placebo reported SAEs. Suicidal ideation was the most common SAE (3 [0.5%] in patients treated with LDMP, 0 with placebo), followed by appendicitis (2 [0.3%] LDMP, 0 placebo) (**Table 4-6**). Other SAEs occurred in 1 patient each. Fractures were reported as SAEs in 3 (0.5%) patients treated with placebo, 0 with LDMP. In addition to the 3 SAEs of suicidal ideation, 1 patient had an SAE of suicide attempt in the LDMP group (see Sections 4.10.1 and 4.10.2).

Table 4-6 Serious adverse events reported in ≥1 patient in either group, All Controlled Studies Pool

MedDRA System Organ Class Preferred Term	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with ≥1 TEAE	9 (1.4)	14 (2.2)
Suicidal ideation	0 (0.0)	3 (0.5)
Appendicitis	0 (0.0)	2 (0.3)
Arteriosclerosis coronary artery[a]	0 (0.0)	1 (0.2)
Cardio-respiratory arrest[a]	0 (0.0)	1 (0.2)
Abdominal pain	0 (0.0)	1 (0.2)
Dysphagia	0 (0.0)	1 (0.2)
Biliary dyskinesia	0 (0.0)	1 (0.2)
Cholecystitis	1 (0.2)	1 (0.2)
Sinusitis	0 (0.0)	1 (0.2)
Arthritis	0 (0.0)	1 (0.2)
Suicide attempt	0 (0.0)	1 (0.2)
Asthma	0 (0.0)	1 (0.2)
Abdominal distension	1 (0.2)	0 (0.0)
Colitis	1 (0.2)	0 (0.0)
Gastrointestinal hemorrhage	1 (0.2)	0 (0.0)
Chest pain	1 (0.2)	0 (0.0)
Clostridium difficile colitis	1 (0.2)	0 (0.0)
Acetabulum fracture	1 (0.2)	0 (0.0)
Femur fracture	1 (0.2)	0 (0.0)
Upper limb fracture	1 (0.2)	0 (0.0)
Osteoarthritis	1 (0.2)	0 (0.0)
Endometrial cancer	1 (0.2)	0 (0.0)
Squamous cell carcinoma	1 (0.2)	0 (0.0)

[a]These 2 SAEs occurred in the patient who died.
Patients counted only once within each preferred term, using the event with the worst-case relationship.
TEAE=treatment-emergent adverse event.

In the 13 LDMP-treated patients with nonfatal SAEs, treatment was discontinued in 4 (1 each with suicidal ideation, suicide attempt, biliary dyskinesia, and abdominal pain), and was interrupted in 3 (1 patient with sinusitis and 2 with appendicitis). All of these SAEs in the LDMP group resolved without sequelae. In placebo-treated patients with SAEs, study drug was discontinued in 1 (GI hemorrhage) and interrupted in 3 (1 each with upper limb fracture, cholecystitis, and abdominal distension).

Of the 14 LDMP-treated patients with SAEs, 13 had participated in the 24-week N30-004 study, and 1 in the 12-week N30-003 study (the latter being the single death; Section 4.8). Among the 9 placebo-treated patients with SAEs, 1 had participated in the N30-002 study, 1 in N30-003, and 7 in N30-004. The SAE imbalance in the LDMP group in the N30-004 study did not appear to

result from the longer treatment duration, because similar numbers of patients had SAE onset prior to the 12-week time point (n=6) as after 12 weeks (n=7); also, there was no apparent trend in the type of SAEs by time of onset.

4.8 Deaths

One death occurred in the clinical program in the LDMP group. She was a 55-year-old obese African American woman with a history of uncontrolled hypertension and hypercholesterolemia who presented 68 days after starting the trial with severe arterial hypoxemia and several days of shortness of breath. She was determined to be in acute respiratory failure with evidence of hypertension-mediated pulmonary edema and hypertensive cardiovascular disease. She died of acute respiratory failure, and the death was deemed by the investigator to be unrelated to study drug.

4.9 Overall Adverse Events

A similar incidence of AEs, related AEs (definitely, probably, possibly, or remotely related to study drug based on the investigator's assessment), and severe AEs was reported in both treatment groups in the All Controlled Studies Pool. A total of 50.4% of patients treated with LDMP and 47.0% with placebo reported at least 1 AE; 19.5% and 17.6%, respectively, had AEs considered related to study drug. Most of the AEs were mild or moderate in intensity (**Table 4-7**).

Table 4-7 Overall adverse events, All Controlled Studies Pool

Category	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with any TEAE	301 (47.0)	320 (50.4)
Patients with any related TEAE	113 (17.6)	124 (19.5)
Patients with any severe TEAE	23 (3.6)	25 (3.9)
Patients with any related severe TEAE	9 (1.4)	6 (0.9)
Patients with study drug discontinuation due to TEAE	21 (3.3)	28 (4.4)
Patients with study drug discontinuation due to a related TEAE	15 (2.3)	18 (2.8)
Patients with dose interruption due to a TEAE	6 (0.9)	6 (0.9)
Patients with dose interruption due to a related TEAE	1 (0.2)	0 (0.0)

Patients are counted only once within each category. If there is more than 1 event within the category, the worst-case assessment is tabulated.
Related AEs include possibly, probably, or definitely related based on investigator assessment.
TEAE=treatment-emergent adverse event.

No severe AE was reported by more than 2 patients in the LDMP group. Severe AEs reported in 2 patients in the LDMP group with at least twice the incidence compared with placebo were sinusitis, abdominal pain, appendicitis, and oropharyngeal pain (2 [0.3%] in patients treated with LDMP and 0 with placebo for each).

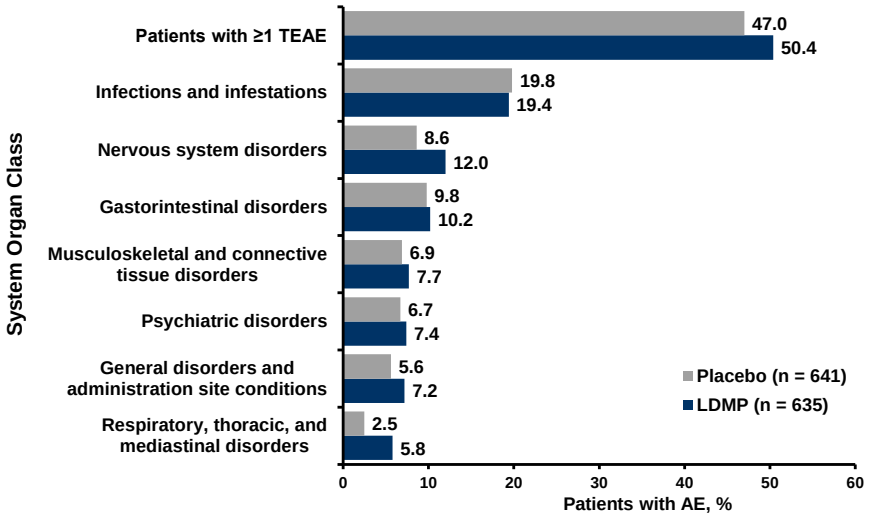
The related AEs reported in ≥1% of patients in the LDMP group and with at least twice the incidence of the placebo group included fatigue (2.8% LDMP, 0.9% placebo), nausea (2.4%, 0.6%), dizziness (1.6%, 0.6%), and diarrhea (1.1%, 0.5%).

Adverse events led to study drug discontinuation in 4.4% of patients treated with LDMP and 3.3% with placebo in the All Controlled Studies Pool. However, in the LDMP group, the most frequently reported AEs resulting in discontinuation occurred in only 2 patients (0.3%) each and included abdominal pain (compared with 0 in the placebo group), herpes zoster (0 placebo), disturbance in attention (1 placebo), headache (1 placebo), anxiety (4 placebo), and suicidal ideation (0 placebo). In the placebo group, anxiety was the AE that most often led to study drug discontinuation (2 LDMP [0.3%], 4 placebo [0.6%]). Three AEs that led to study drug discontinuation in the LDMP group were also SAEs. There was an equal number of study drug interruptions in each treatment group. Three AEs that led to treatment interruption in the LDMP group were also SAEs.

In addition, 2 patients treated with LDMP and 3 with placebo were discontinued due to an AE, but were not reported as such. This occurred because the study drug discontinuation was captured on a separate case report form (CRF) page than study discontinuation (AE CRF and study termination CRF pages, respectively). One additional patient discontinued during the placebo run-in phase.

Figure 4-1 shows adverse events by system-organ-class (SOC) reported in at least 5% of patients. Only 1 SOC, respiratory, thoracic and mediastinal disorders, had at least twice the incidence in the LDMP group compared with the placebo group (5.8% vs 2.5%).

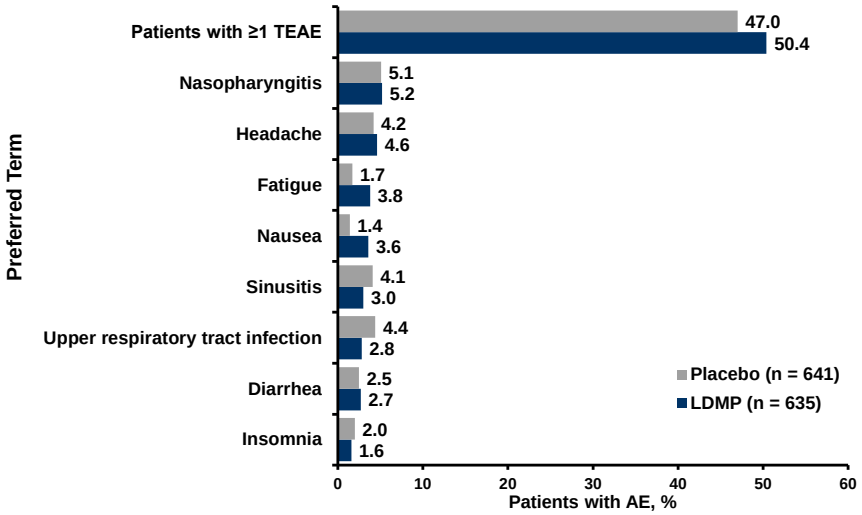
Figure 4-1 Adverse events by system-organ-class (>5% of patients), All Controlled Studies Pool



Patients are counted only once within each category.
TEAE=treatment-emergent adverse event.

Figure 4-2 shows the most commonly reported AEs in at least 2% of patients in either treatment group in the All Controlled Studies Pool. Only 2 of these events, fatigue (3.8% LDMP, 1.7% placebo) and nausea (3.6%, 1.4%) had at least twice the incidence in the LDMP compared with the placebo group.

Figure 4-2 Most commonly reported adverse events (>2% of patients in either group), All Controlled Studies Pool



Patients are counted only once within each category.
TEAE=treatment-emergent adverse event.

In the Phase 3 Studies Pool, the AEs reported in ≥2% of patients in the LDMP group with at least twice the incidence in the placebo group were nausea (3.8% LDMP, 1.4% Placebo), fatigue (3.4%, 1.5%), and dizziness (2.0%, 0.8%).

For the commonly reported AEs (see **Figure 4-2**), headache, fatigue, nausea, and diarrhea occurred primarily within the first 4 weeks of treatment; there was evidence of adaptation with continued therapy. Insomnia, nasopharyngitis, sinusitis, and upper respiratory tract infection tended to occur throughout the study. There were no trends in the incidence or types of AEs with an onset prior to versus after the 12-week time point.

A total of 235 patients treated with LDMP (218 with placebo) completed 24 weeks of treatment in the N30-004 study. The safety data through 24 weeks of treatment indicated no new safety issues specific to, or associated with, LDMP treatment.

4.10 Adverse events of special interest

Adverse events of special interest were based on the product labeling of SSRIs and SNRIs. These included the boxed warning for risk of suicidal ideation and behavior with antidepressants (Paxil PI, Pexeva PI). Other events of interest captured in the SSRI class labeling include serotonin

syndrome, hyponatremia, GI or other bleeding, bone fracture, activation of mania/hypomania, seizures, akathisia, hallucinations, and sexual dysfunction (Paxil PI, Pexeva PI). Noven also assessed cardiovascular and hepatic events based on uncommon reports with the SNRI desvenlafaxine (Clayton et al 2006). Weight gain and sexual function, issues of concern in this patient population, and the potential for withdrawal symptoms following treatment discontinuation were also evaluated.

4.10.1 Serious adverse events associated with warnings in labels of SSRIs and SNRIs

Few patients in either treatment group had AEs associated with warnings in labels of SSRIs and SNRIs that were considered serious (**Table 4-8**). Two cardiovascular SAEs were reported in a patient treated with LDMP (which the investigator considered as not related to study drug) and 1 with placebo (see Section 4.7). No GI or other types of bleeding events were reported as SAEs. Three patients treated with LDMP and none with placebo had bone fracture SAEs. In the LDMP group, suicidality SAEs included 1 suicide attempt and 3 cases of suicidal ideation which were elicited through responses on the STS questionnaire (see Sections 4.7 and 4.10.2).

Table 4-8 Serious adverse events associated with warnings in labels of SSRIs and SNRIs, All Controlled Studies Pool

	Placebo N=641 n (%)	LDMP 7.5mg N=635 n (%)
Cardiovascular events	1 (0.2)	2 (0.4)
GI bleeding/Any bleeding	0 (0.0)	0 (0.0)
Fractures	3 (0.5)	0 (0.0)
Suicidality		
Completed suicide	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	1 (0.2)
Self-injurious behavior	0 (0.0)	0 (0.0)
Spontaneous suicidal ideation	0 (0.0)	0 (0.0)
Scale-elicited suicidal ideation	0 (0.0)	3 (0.5)

SNRIs=serotonin-norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors.

4.10.2 Suicidality

Suicidality was prospectively evaluated in all of the studies. Data from the LDMP clinical development program indicate that patients treated with LDMP 7.5 mg for VMS associated with menopause have no increase in suicide risk compared to the background rate for this population. There were no completed suicides in the LDMP clinical development program. Four cases of suicidality were reported in the LDMP group as SAEs, and none in the placebo group. All four cases occurred in Study N30-004 and comprise 1 patient who attempted suicide and 3 patients who had elevated scores on the STS scale that were reported as SAEs. Not all reports of increased STS scores within Study N30-004 were reported as SAEs. Based on an STS total score of >0 at post-baseline assessment, there were a total of 16 events of STS-emergent suicidal

ideation or behavior in the LDMP group and 12 events in the placebo group. There was no scale-emergent elevation in Study N30-003, which used the C-SSRS.

The STS has been shown to be a sensitive instrument for identifying clinical trial patients with suicidal thoughts and behavior. As a self-reported instrument, it may be more sensitive than rater-administered assessments (Coric et al, 2009). In September 2010, FDA issued a guidance document, "Suicidality: Prospective Assessment in Clinical Trials," which recommended use of the rater-administered C-SSRS for prospective suicidality assessments in clinical trials of drugs with central nervous system (CNS) activity. Study N30-003, designed after the issuance of this guidance, utilized the C-SSRS.

There were no events of C-SSRS-emergent suicidal ideation or behavior in N30-003 at any post-baseline assessment in either treatment group.

Upon learning of the cases of suicidality in Study N30-004, Noven established an independent Safety Monitoring Committee of qualified physicians tasked with reviewing relevant safety data and recommending any modification to the studies based on their assessment. No event occurred that required the committee to meet. After completion of the studies, all suicidality cases were assessed by the Chair of the Safety Monitoring Committee. His report concluded that the rates of suicidal ideation or behavior are in line with, or actually below, what may be expected in the general population of women in this age group over a period of nearly 6 months (Crosby et al 2011).

4.10.3 Cardiovascular events

In the All Controlled Studies Pool, 4.3% of patients treated with LDMP and 2.7% with placebo had cardiovascular AEs (**Table 4-9**). Approximately half the patients with cardiovascular AEs had a cardiovascular medical history (14 of 27 treated with LDMP, and 8 of 17 with placebo). In the LDMP group, hypertension was the most common cardiovascular event (1.1% LDMP, 0.5% placebo), and most of the affected patients had a history of hypertension (5 of 7 treated with LDMP, and 2 of 3 with placebo). In the placebo group, blood pressure increased was the most common event (0.2% LDMP, 1.1% placebo). Two of 7 patients with blood pressure increase in the placebo group (and 0 of 1 in LDMP group) had a history of hypertension. Hypertension was reported as an AE based on a diagnosis, whereas blood pressure increased was based on the patient's blood pressure measurement.

One patient with cardio-respiratory arrest and coronary artery arteriosclerosis died, and the investigator determined these events were not related to LDMP treatment (Section 4.8). No other cardiovascular events as SAEs, or clinically important cardiovascular findings in the LDMP group were reported. Chest discomfort in an LDMP-treated patient was the only cardiovascular event resulting in study drug discontinuation.

Table 4-9 Treatment-emergent cardiovascular events, All Controlled Studies Pool

MedDRA System Organ Class Preferred Term	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with ≥1 TEAE	17 (2.7)	27 (4.3)
Hypertension	3 (0.5)	7 (1.1)
Chest pain	1 (0.2)	4 (0.6)
Edema peripheral	1 (0.2)	4 (0.6)
Palpitations	2 (0.3)	3 (0.5)
Electrocardiogram abnormal	1 (0.2)	3 (0.5)
Blood pressure increased	7 (1.1)	1 (0.2)
Arrhythmia	0 (0.0)	1 (0.2)
Arteriosclerosis coronary artery[a]	0 (0.0)	1 (0.2)
Cardio-respiratory arrest[a]	0 (0.0)	1 (0.2)
Ventricular dysfunction	0 (0.0)	1 (0.2)
Chest discomfort[b]	0 (0.0)	1 (0.2)
Cardiac murmur	0 (0.0)	1 (0.2)
Electrocardiogram QT prolonged	0 (0.0)	1 (0.2)
Heart rate increased	0 (0.0)	1 (0.2)
Heart rate irregular	0 (0.0)	1 (0.2)
Arrhythmia supraventricular	1 (0.2)	0 (0.0)
Bradycardia	1 (0.2)	0 (0.0)
Carotid bruit	1 (0.2)	0 (0.0)
Hypotension	1 (0.2)	0 (0.0)

[a]These 2 events occurred in the same patient and led to death (Study N30-003).
[b]This event led to discontinuation of study drug (Study N30-004).
A patient is counted only once within each preferred term, using the event having the worst-case relationship.
MedDRA=Medical Dictionary for Regulatory Activities; TEAE= treatment-emergent adverse event.

4.10.4 Hepatic events

Patients treated with LDMP had no clinically important hepatic events or hepatic events reported as SAEs or leading to study drug discontinuation. The incidence of hepatic AEs was low and similar in both treatment groups in the All Controlled Studies Pool (**Table 4-10**).

Table 4-10 Treatment-emergent hepatic events, All Controlled Studies Pool

MedDRA System Organ Class Preferred Term	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with ≥1 TEAE	6 (0.9)	3 (0.5)
Liver function test abnormal	0 (0.0)	2 (0.3)
Transaminases increased	0 (0.0)	1 (0.2)
Alanine aminotransferase increased	4 (0.6)	0 (0.0)
Hepatic enzyme increased	2 (0.3)	0 (0.0)

Patients counted only once within each preferred term, using the event having the worst-case relationship.
TEAE=treatment-emergent adverse event.

There was a low incidence of potentially clinically significant increases (≥5 × upper limit of normal [ULN]) in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which was similar across treatment groups. A total of 4 cases of ALT increase (3 patients [0.5%] treated with LDMP and 1 [0.2%] with placebo) and 3 cases of AST increase (2 [0.3%] LDMP, 1 [0.2%] placebo) were recorded. Two of these patients (1 LDMP, 1 placebo) had a potentially clinically significant increase in both ALT and AST at the end of study. No patients with ALT and/or AST increase had an increase in bilirubin value.

4.10.5 Gastrointestinal bleeding or other bleeding events

Gastrointestinal bleeding or other bleeding events occurred in 1.9% of patients treated with LDMP and 1.6% with placebo, and there was no clear trend in the types of events in the two groups (**Table 4-11**). Five patients discontinued treatment for GI or bleeding events (2 treated with LDMP, 3 with placebo). The LDMP-treated patients who discontinued had gingival bleeding (n=1) and vaginal hemorrhage (n=1).

Concomitant nonsteroidal anti-inflammatory drug (NSAID) use did not appear to affect the risk of GI bleeding or other bleeding events. While some reports of increased risk with concomitant SSRI and NSAID use have been published (Weinrieb et al 2005), no clinically relevant findings resulted from this analysis.

Table 4-11 Treatment-emergent gastrointestinal or bleeding events, All Controlled Studies Pool

MedDRA System Organ Class Preferred Term	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with ≥1 TEAE	10 (1.6)	12 (1.9)
Vaginal hemorrhage[a]	3 (0.5)	6 (0.9)
Vitreous hemorrhage	0 (0.0)	1 (0.2)
Gingival bleeding[b]	0 (0.0)	1 (0.2)
Rectal hemorrhage	0 (0.0)	1 (0.2)
Periorbital hematoma	0 (0.0)	1 (0.2)
Breast hematoma	0 (0.0)	1 (0.2)
Epistaxis	0 (0.0)	1 (0.2)
Postmenopausal hemorrhage	3 (0.5)	0 (0.0)
Duodenal ulcer	1 (0.2)	0 (0.0)
Gastric ulcer	1 (0.2)	0 (0.0)
Gastrointestinal hemorrhage[c]	1 (0.2)	0 (0.0)
Hematemesis	1 (0.2)	0 (0.0)
Bloody discharge[d]	1 (0.2)	0 (0.0)
Helicobacter infection[c]	1 (0.2)	0 (0.0)

[a]Vaginal hemorrhage led to study drug discontinuation in 2 patients (1 in each treatment group).
[b]Gingival bleeding led to study drug discontinuation in 1 LDMP-treated patient.
[c]Gastrointestinal hemorrhage and helicobacter infection led to study drug discontinuation in 1 placebo-treated patient.
[d]Bloody discharge led to study drug discontinuation in 1 placebo-treated patient.
Patients counted only once within each preferred term, using the event with the worst-case relationship.
TEAE=treatment-emergent adverse event.

4.10.6 Other known adverse events of SSRIs

Other AEs that have been associated with SSRIs, including serotonin syndrome, hyponatremia, bone fracture, activation of mania/hypomania, seizures, akathisia, and hallucinations, were assessed. None was reported in ≥1% of patients treated with LDMP and with at least twice the incidence of placebo.

4.10.7 Weight and body mass index

There were no clinically relevant differences in body weight and BMI values over time, or in shifts in body weight and BMI (per CTCAE criteria) between treatment groups in the All Controlled Studies Pool.

An exploratory analysis of body weight change in the individual Phase 2 and 3 studies showed a significant difference in patients receiving LDMP compared with placebo at Week 4 in each study; however, mean weight at Week 4 in patients treated with LDMP was unchanged from baseline and statistically significantly less than that with placebo (a small mean increase in

weight was observed in the placebo group). There was no significant difference at Week 12 (**Table 4-12**).

Furthermore, an exploratory analysis examined weight gain of at least 7%, a generally accepted criterion of clinically significant weight gain in patients receiving SSRIs or other antidepressants (Fava et al 2000, Sussman and Ginsberg 1998, Sussman et al 2001). There was no significant difference between the LDMP and placebo groups at Week 4 or 12 in the N30-003 and N30-004 studies, or at Week 24 in the N30-004 study for weight gain of at least 7%. Findings in the Phase 2 N30-002 study supported the Phase 3 study results.

Table 4-12 Weight (lb) results summary over time, Safety Population, All Controlled Studies Pooled

		Placebo N=641		LDMP 7.5 mg N=635	
Visit	**Statistic**	**Result**	**Change**	**Result**	**Change**
Baseline	n	641		635	
	Mean (SD)	170.6 (35.8)	n/a	169.9 (35.8)	n/a
	Median (Min, Max)	166.6 (95, 339)		164.2 (83, 387)	
Day 7	n	51	51	48	48
	Mean (SD)	164.2 (36.4)	0.5 (4.40)	166.6 (35.1)	0.2 (6.78)
	Median (Min, Max)	156.5 (95, 254)	0.0 (-11, 25)	163.6 (104, 252)	-0.2 (-7, 43)
Day 14	n	326	326	321	321
	Mean (SD)	174.4 (38.0)	0.1 (2.44)	171.9 (38.0)	0.1 (2.89)
	Median (Min, Max)	168.8 (102, 340)	0.0 (-19, 7)	166.7 (79, 385)	0.0 (-11, 14)
Day 28	n	601	601	602	602
	Mean (SD)	171.0 (36.3)	0.6 (4.21)	169.7 (35.8)	-0.0 (3.49)
	Median (Min, Max)	167.5 (97, 340)	0.2 (-22, 50)	164.0 (82, 385)	0.0 (-13, 40)
Day 57	n	52	52	49	49
	Mean (SD)	166.0 (36.0)	2.1 (8.86)	165.5 (34.4)	-0.5 (7.98)
	Median (Min, Max)	164.9 (96, 260)	0.1 (-13, 49)	160.0 (100, 251)	-1.5 (-15, 45)
Day 84	n	528	528	541	541
	Mean (SD)	172.3 (36.5)	0.8 (5.80)	170.9 (36.6)	0.5 (4.61)
	Median (Min, Max)	166.8 (100, 338)	1.0 (-50, 53)	165.0 (83, 390)	0.2 (-14, 14)
Day 169	n	268	268	270	270
	Mean (SD)	166.9 (33.5)	0.2 (7.66)	168.1 (32.7)	0.5 (6.50)
	Median (Min, Max)	163.0 (102, 277)	0.2 (-42, 48)	162.0 (111, 266)	0.9 (-30, 20)

Change from baseline is based on patients with both a baseline and a post-baseline value.
n/a = not applicable; Max=maximum; Min=minimum; SD=standard deviation.

4.10.8 Evaluation of sexual dysfunction

Based on review of AEs, LDMP treatment did not adversely affect sexual function. No AE suggestive of sexual dysfunction occurred in ≥1% of patients treated with LDMP, and the

incidence of events was similar in both treatment groups in the All Controlled Studies Pool (**Table 4-13**).

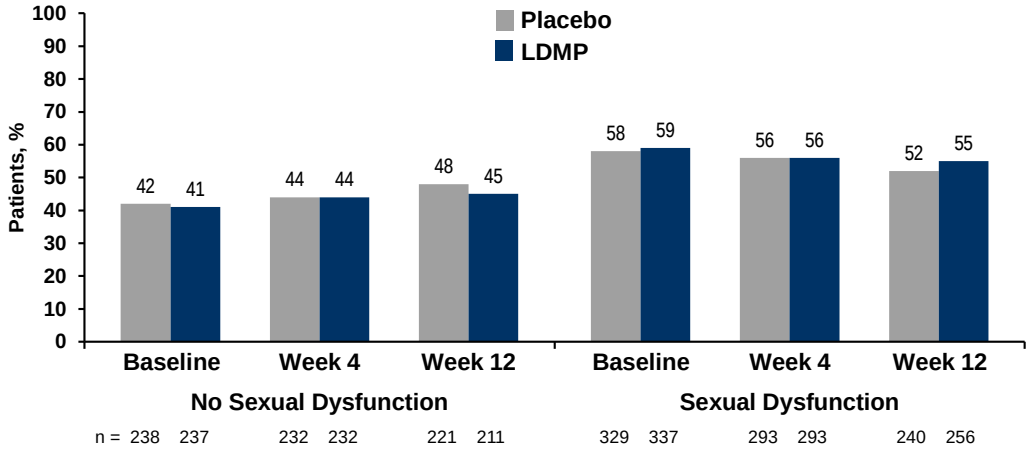
Table 4-13 Treatment-emergent sexual dysfunction, All Controlled Studies Pool

MedDRA System Organ Class Preferred Term	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
Patients with ≥1 TEAE	4 (0.6)	3 (0.5)
Libido decreased	2 (0.3)	1 (0.2)
Anorgasmia	1 (0.2)	1 (0.2)
Sexual dysfunction	0 (0.0)	1 (0.2)
Loss of libido	1 (0.2)	0 (0.0)

Patients are counted only once within each preferred term, using the event with the worst-case relationship.
MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

Sexual function was also assessed using the ASEX rating scale (Section 4.1.3). In the Phase 3 Studies Pool (mITT population, N=1174), there was no significant difference for the proportions of LDMP and placebo patients reporting sexual dysfunction at any time point (**Figure 4-3**). At 24 weeks in Study N30-004, 56% of patients treated with LDMP and 57% with placebo reported sexual dysfunction. Furthermore, no significant difference was shown between the LDMP and placebo groups in the ASEX total score or any of the 5 items across Weeks 4 and 12 (in N30-003 and N30-004 studies), and 24 (N30-004 study). Individual study analyses were consistent with that of the Phase 3 Studies Pool.

Figure 4-3 Sexual dysfunction by ASEX, Pooled Phase 3 Studies (N30-003, N30-004)[a]

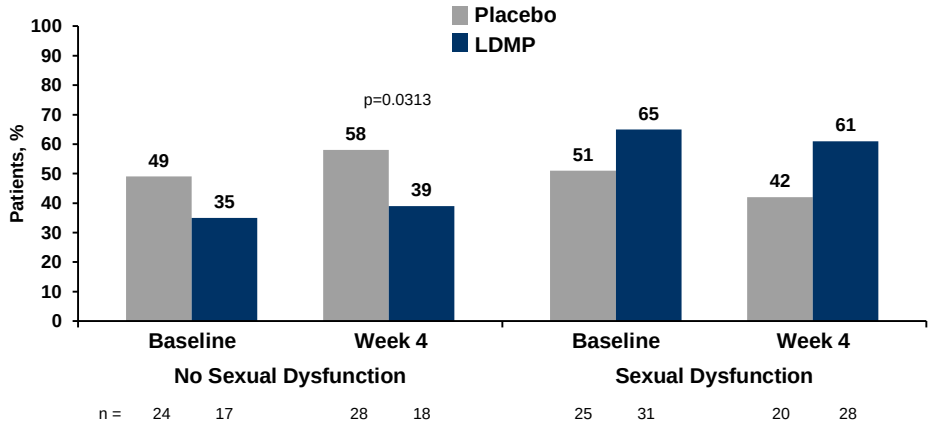


[a]mITT population in Phase 3 Studies Pool (N=1174).
ASEX=Arizona Sexual Experience Scale; mITT, modified intent-to-treat.

In contrast to findings in the Phase 3 studies, a significant difference (p=0.0313) in sexual function favoring placebo was shown at Week 4 in the Phase 2 (N30-002) study (mITT

population, N=99) (**Figure 4-4**). However, more patients treated with LDMP than placebo reported sexual dysfunction (65% and 51%, respectively) at baseline, which decreased at Week 4 but to a lesser degree in the LDMP group (61% and 42%, respectively); also, a relatively small number of patients reported sexual dysfunction in each treatment group. Therefore, this difference in sexual function between treatment groups in the Phase 2 study was not considered clinically relevant.

Figure 4-4 Sexual dysfunction by ASEX, Study N30-002[a]



[a]mITT population in Phase 2 Study N30-002 (N=99).
ASEX=Arizona Sexual Experience Scale; mITT, modified intent-to-treat.

4.10.9 Discontinuation-emergent signs and symptoms

There were no meaningful differences between the LDMP and placebo groups in the symptoms patients experienced within 7 days after stopping treatment. These findings support the ability of patients to discontinue LDMP treatment without the need for dose reductions. In the All Controlled Studies Pool, 17.6% of patients treated with LDMP and 13.7% with placebo had at least 1 new symptom that appeared after study drug discontinuation and within the 7 days prior to administration of the DESS; 20.6% and 19.7%, respectively, had no symptoms in the 7-day post treatment period. Old symptoms that appeared before the 7 days prior to administration of the DESS, were present while taking study drug, and continued into the 7-day post treatment period were most likely to remain unchanged or to improve than to worsen (**Table 4-14**).

Table 4-14 Discontinuation-emergent signs and symptoms, Safety Population, All Controlled Studies Pool

DESS Category[a]	Number of symptoms	Placebo N=641 n (%)	LDMP 7.5 mg N=635 n (%)
New symptoms	0	429 (66.9)	394 (62.0)
	≥1	88 (13.7)	112 (17.6)
Old symptom (any category)	≥1	414 (100.0)	405 (100.0)
Old symptom (but worse)	≥1	73 (17.6)	102 (25.2)
Old symptom (but improved)	≥1	127 (30.7)	139 (34.3)
Old symptom (but unchanged)	≥1	376 (90.8)	356 (87.9)
Symptom not present	0	2 (0.3)	2 (0.3)
	≥1	515 (80.3)	504 (79.4)

[a]Patients are counted only once per category. Patients with multiple signs or symptoms are counted in each category that applies.
DESS=discontinuation-emergent signs and symptoms.

The most commonly reported new symptom was increased dreaming or nightmares, reported by 31/635 (4.9%) patients treated with LDMP and 20/641 (3.1%) with placebo. New symptoms reported in ≥2% of patients treated with LDMP and at twice the incidence compared with placebo were muscle cramps, spasms, or twitches (3.5% LDMP, 1.4% placebo); restless feeling in the legs (2.5%, 1.1%); and trouble sleeping, insomnia (2.4%, 1.1%). No new symptom appeared in ≥5% of patients treated with LDMP. The worsening symptom reported most commonly was sweating more than usual, reported by 57/635 (9.0%) and 33/641 (5.1%) patients treated with LDMP and placebo, respectively. No worsening symptom was reported at more than twice the incidence with LDMP versus placebo.

4.11 Clinical laboratory and hematology evaluations

Analysis of clinical chemistry assessments showed a low incidence of potentially clinically significant results that was similar for the LDMP and placebo groups in the All Controlled Studies Pool. The parameters analyzed included albumin, alkaline phosphatases, ALT, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatine kinase, creatinine, plasma glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, and uric acid. (See Section 4.10.4 for more information on patients with ALT and/or AST increase.) Overall, there were no clinically relevant differences in hematology parameters between the LDMP and placebo groups.

4.12 Electrocardiograms

In the All Controlled Studies Pool, ECG results were similar for the LDMP and placebo groups and no clinically relevant changes were observed between the groups.

4.13 Vital signs

Overall, there were no clinically relevant differences in vital signs between treatment groups in the All Controlled Studies Pool. In general, the mean values for vital signs remained within normal ranges throughout the study. The mean pulse rates in the LDMP group were 71.1 bpm at baseline and 69.7 bpm at the end of study, and in the placebo group were 70.6 and 70.4 bpm, respectively. The mean systolic/diastolic blood pressure measurements in the LDMP group were similar at baseline (121.3/76.2 mm Hg) and at the end of study (122.1/76.5 mm Hg). The corresponding values in the placebo group were 122/0/76.2 mm Hg and 121.9/76.3 mm Hg, respectively. Approximately 1% of patients in both treatment groups had potentially clinically significant increases in systolic and diastolic blood pressure measured at screening or at the end of study (**Table 4-15**). There were no potentially clinically significant increases in body temperature.

Table 4-15 Incidence of potentially clinically significant vital signs,[a] All Controlled Studies Pooled, Safety Population

	Placebo N=641 n (%)		LDMP 7.5 mg N=635 n (%)	
Parameter	**Screening**	**End of Study**	**Screening**	**End of Study**
Systolic blood pressure (mmHg)	6 (0.9)	9 (1.4)	6 (0.9)	7 (1.1)
Diastolic blood pressure (mmHg)	6 (0.9)	5 (0.8)	6 (0.9)	7 (1.1)

[a]Per Common Terminology Criteria for Adverse Events (CTCAE).

4.14 Drug interactions

No new drug interaction studies were conducted in the LDMP clinical development program. The proposed labeling for drug interactions of LDMP 7.5 mg once daily, in taking a conservative approach, will reflect the labeling of Pexeva, which is approved for use in psychiatric conditions at doses ranging from 10 to 60 mg/day.

4.15 Analyses of subgroups

The safety of LDMP was generally similar in all subgroups analyzed in the All Controlled Studies Pool. Results showed no clinically relevant differences as a function of age, race, or ethnicity.

4.16 Postmarketing analyses

LDMP 7.5 mg once daily is a lower dose of the same compound (paroxetine mesylate) that is approved for use in psychiatric conditions at doses ranging from 10 to 60 mg/day and marketed under the brand name Pexeva. In addition, Noven's 505(b)(2) NDA for LDMP relies on FDA's findings of safety for Paxil (paroxetine hydrochloride). As Paxil has been approved since 1992,

the safety profile of paroxetine has been well established and is reflected in the Paxil, Pexeva, and proposed LDMP labeling.

Noven submits to FDA an Annual Adverse Drug Experience Report for Pexeva (paroxetine mesylate) which presents the postmarketing safety experiences observed with its use at doses of 10 to 60 mg/day. In addition to the search of the paroxetine literature for possible cases that are captured in the Pexeva Annual Adverse Drug Experience Report, Noven conducted an additional literature search for safety events related to paroxetine use in nonpsychiatric patients to identify data that may have potential relevance to the safety assessment of LDMP. The report was run over MEDLINE, EMBASE, and BIOSIS through the Dialog search platform, covering the period from 1992 (initial approval of Paxil) through December 2012. The literature search did not reveal any previously unidentified AEs reported with paroxetine treatment.

The 4 month safety update (4MSU) submitted to the LDMP NDA included the Pexeva Annual Adverse Drug Experience Report covering adverse events reported in the period from July 2011 to July 2012. In addition, it included a literature search covering the period from July to December 2012, and an additional literature search for safety events related to paroxetine use in nonpsychiatric patients for the period March to December 2012. Based on these searches, there was no significant change in the safety of Pexeva compared with previous reporting periods.

A review of the 2012, 2nd quarter (Q2) release of the Adverse Event Reporting System (AERS) database showed that case reports for female paroxetine users aged 40 to 65 years were similar between the two dosing groups of 10 mg and >10 mg with respect to (i) age; (ii) top 15 indications for use; (iii) menopause-related indications for use; and (iv) primary outcome. When signals of disproportionality were examined, the events of interest for the top 15 scores that met the signal threshold were not remarkably different between the two dosing groups, but the >10 mg group had disproportionality scores that were much higher than those reported for the 10 mg group.

When examining Preferred Terms of interest relating to major cardiovascular events, suicidality, abnormal bleeding, and bone fracture, differences were found between the 10 mg and >10 mg dosing groups with respect to suicidality, with the number and strength of the signals being higher in the >10 mg dose group. No conclusions could be drawn from the abnormal bleeding terms of interest as different signals met the threshold in the different dosing groups. There were no signals that met the significance threshold among the serious cardiac events or the bone fracture-related terms of interest for either dosing group (see Appendix U).

4.17 Safety summary

In the clinical development program, LDMP 7.5 mg once daily demonstrated tolerability and favorable safety compared to placebo in the population of patients treated for moderate to severe VMS associated with menopause. No new or unexpected safety findings were observed.

Additionally, there was no increase in mean weight gain, sexual dysfunction, or discontinuation symptoms in patients treated with LDMP compared with placebo.

The most common AEs experienced by patients treated with LDMP were consistent with the known safety profile of paroxetine, and most occurred at a lower incidence than observed in clinical trials of patients treated with paroxetine for psychiatric indications, as outlined in the Paxil and Pexeva US package inserts (Paxil PI, Pexeva PI).

The overall incidence of AEs was similar in patients treated with LDMP or placebo, and most AEs were mild to moderate in intensity. Patients in both treatment arms had a low incidence of SAEs associated with warnings in labels of SSRIs and SNRIs. There were no clinically important findings with respect to cardiovascular events, and no difference between treatment groups in the incidence and type of GI or bleeding AEs.

The safety profile of paroxetine has been well characterized in over 20 years of use. The LDMP clinical development program generated safety data for a lower dose of paroxetine in a new population, which demonstrated that LDMP was well tolerated.

5 RISK MANAGEMENT

The safety profile of paroxetine has been well characterized, as described above. The LDMP program captured safety data with a 7.5 mg dose of paroxetine mesylate in postmenopausal women with VMS, which is described in the Adverse Events section of the proposed USPI. In addition, the proposed LDMP label adopts the class SSRI warnings and precautions. With a focus on the latter, Noven has developed a risk management plan to ensure the safe and appropriate use of LDMP. The elements of the risk management plan are as follows:

Label

Noven has adopted the class safety labeling for antidepressants (including SSRIs) and safety warnings and precautions for paroxetine in the proposed label for LDMP. Thus, the proposed LDMP USPI includes the following safety information from the Pexeva label:

- Boxed warning for suicidality
- Warnings and precautions addressing: interaction with tamoxifen, abnormal bleeding, potential for interaction with MAOIs, serotonin syndrome, hyponatremia, bone fracture, use with drugs containing paroxetine, mania and hypomania, seizures, akathisia, use in pregnancy, and use in patients with concomitant illness
- Contraindications for concomitant use with MAOIs, thioridazine, and pimozide
- Language in the dosing and administration section regarding use with MAOIs and linezolid or methylene blue

- List of drug interactions with paroxetine

Medication guide

Noven proposes that patients prescribed LDMP also receive a medication guide alerting them to the known risks and precautions associated with the use of paroxetine. With a focus on the warnings and precautions described in the USPI, the medication guide describes these risks to the patient.

Regarding the boxed warning for suicidality, the medication guide provides the patient with a list of symptoms that may be indicative of suicidal thinking and should be communicated to a healthcare provider right away. Similarly for the other warnings and precautions in the USPI, the medication guide highlights symptoms and information the patient should be aware of and share with their healthcare provider.

To avoid off-label use of LDMP for depression or other psychiatric indications, and to avoid medication errors, the proposed LDMP USPI and medication guide were written to ensure physicians and patients are aware that LDMP was studied only for VMS.

Pharmacovigilance

Noven will perform pharmacovigilance activities, which include the collection of adverse event reports from multiple sources, the review and monitoring of these data, and evaluation for a potential signal.

Enhanced pharmacovigilance

In addition to the pharmacovigilance activities described above, Noven is also planning to conduct enhanced pharmacovigilance for AEs of special interest, such as suicidality, abnormal bleeding, and bone fracture. New cases of these events reported with LDMP will be queried for the following elements in an attempt to obtain a complete picture of the event:

- Symptoms experienced and date of onset
- Clinical outcome
- Duration of LDMP therapy
- Start and stop dates for all concomitant medications taken within 6 months of event onset
- Relevant medical history within the past 10 years

This information will be reviewed for a potential signal and shared with FDA on an ongoing basis.

Education plan

The Education Plan will target prescribers, pharmacists, and patients. The education content will reinforce the potential risks captured in the label and the importance of monitoring for these

risks. It will also address that LDMP was studied only in postmenopausal women and should not be used in pregnant women due to the known risks of paroxetine in pregnancy. The content will also include information on the drugs that should not be used concomitantly with LDMP.

Assessment

On an ongoing basis, Noven will assess the appropriateness and effectiveness of risk management activities in consultation with FDA.

6 BENEFIT/RISK ASSESSMENT

LDMP has a favorable benefit/risk profile for the treatment of moderate to severe VMS associated with menopause. An LDMP 7.5 mg capsule given once daily at bedtime is a lower daily dose of paroxetine than is currently approved for psychiatric indications. The LDMP data establish the tolerability and efficacy of 7.5 mg paroxetine mesylate for the treatment of VMS.

6.1 Clinical benefit

LDMP 7.5 mg/day is a nonhormonal agent containing paroxetine mesylate, developed specifically for the treatment of moderate to severe VMS associated with menopause. The efficacy of LDMP dosed once daily at bedtime has been demonstrated in two pivotal Phase 3 trials including 1184 women with moderate to severe VMS associated with menopause. The results of these studies show statistically significant and clinically meaningful benefit in this patient population.

Statistically significant reduction in hot flash frequency compared to placebo was shown in Studies N30-004 and N30-003 at Weeks 4 and 12. Statistically significant reduction in hot flash severity compared to placebo was shown in Study N30-004 at Weeks 4 and 12 and in Study N30-003 at Week 4.

LDMP treatment demonstrated both rapid onset and persistence of benefit. Persistence of benefit was shown in Study N30-004, with significantly more patients treated with LDMP achieving at least a 50% reduction in frequency of moderate to severe hot flashes compared with placebo at Week 24. Analyses of time to onset of hot flash reduction showed significant reductions in frequency of hot flashes in patients treated with LDMP as early as Week 1.

The clinical meaningfulness of the reduction in hot flash frequency with LDMP was supported by the results of an analysis anchored to patient-reported improvement. In addition to the primary and key supportive endpoints, the clinical meaningfulness of the effects of LDMP was further evaluated through a comprehensive set of 19 prespecified secondary analyses. Most notably, LDMP demonstrated improvements compared to placebo at Weeks 4 and 12 in reducing the number of nighttime awakenings due to moderate to severe hot flashes. Exploratory analyses on the most clinically relevant of these endpoints showed a directionality of effect favorable to LDMP, and these results correlate to the findings of the co-primary endpoint analyses.

Findings from subgroup analyses of the primary endpoints consistently favored LDMP compared with placebo. Of 70 subgroup comparisons with a sample size of at least 20 patients per group, 65 (93%) of the comparisons were numerically in favor of LDMP. These results support the effectiveness of LDMP 7.5 mg across age categories, race, ethnicity, BMI, and type of menopause onset.

Taken together, these studies provide substantial evidence for the efficacy of LDMP 7.5 mg once daily at bedtime for the treatment of moderate to severe VMS associated with menopause.

6.2 Risks

The LDMP clinical trial program demonstrated tolerability and a favorable safety profile in the population of patients treated for moderate to severe VMS associated with menopause. In the context of the established safety database for higher doses of paroxetine prescribed for approved psychiatric indications, no new safety signal was observed with LDMP.

From AERS analysis, it appears that certain events of interest and signal scores are greater in the cases of female paroxetine users aged 40 to 65 years reported into AERS in the >10 mg dose group compared to the 10 mg dose group (see Appendix U).

The majority of AEs with LDMP were mild to moderate and did not result in discontinuation. Some patients reported nausea, fatigue, and dizziness, most of which occurred early in the first weeks of treatment and resolved as treatment continued.

Sexual dysfunction and weight gain are side effects of special concern to many patients taking SSRIs. In the LDMP clinical program, the incidence of AEs suggestive of sexual dysfunction was similar in the LDMP and placebo groups, and there were no inter-group differences in ASEX scores. There was no evidence of weight gain compared with placebo.

The incidence of study drug discontinuations due to AEs was 4.4% in the LDMP group compared with 3.3% in the placebo group. However, the most frequently reported AEs resulting in study drug discontinuation in the LDMP group occurred in only 2 patients (0.3%) each. There was no clinically relevant difference in laboratory evaluations, vital signs, body weight, BMI, or ECGs between the LDMP and placebo groups.

The proposed LDMP label will include the full warnings and precautions of higher-dose paroxetine products. Noven will also have a careful risk management strategy in place post-marketing for potential risk factors such as suicidality, abnormal bleeding, and bone fractures. Prescribing physicians will need to keep these in mind when considering this treatment option.

6.3 Benefit/risk conclusion

There is an unmet medical need for additional treatment options for women seeking treatment of their moderate to severe VMS associated with menopause. Currently, HT is the only approved treatment for VMS associated with menopause. Although HT is effective, there are some women

who are unable or unwilling to take HT. Additional, FDA-approved treatment options are needed for women seeking treatment and for physicians.

LDMP is a nonhormonal agent that has demonstrated efficacy out to 24 weeks and a favorable safety and tolerability profile. If approved, LDMP would represent an important new treatment option that may improve the lives of women with moderate to severe VMS.

7 APPENDIX A: PHARMACOLOGY AND PHARMACOKINETICS/DRUG METABOLISM OF LDMP

Study N30-005

This phase 1, open-label, single- and multiple-dose study evaluated the pharmacokinetics, safety, and tolerability of LDMP in postmenopausal, nonsmoking women aged >40 years.

After a 3-week screening period, patients received LDMP 7.5-mg capsules as a single dose on Day 1 and then as multiple doses (once daily for 14 days) on Days 6 to 19. Blood samples were collected predose and up to 120 hours postdose on Day 1 (single-dose pharmacokinetic profile), at predose (after 12 doses) on Day 18 and at predose and up to 24 hours postdose on Day 19 (multiple-dose pharmacokinetic profile). Capsules were taken with 240 mL of water while fasted. Safety was evaluated throughout the study.

The pharmacokinetic metrics resulting from this study are summarized in **Table 7-1**. Steady state was achieved after approximately 12 doses (Day 18). The peak exposure, measured as maximum observed plasma concentration (C_{max}), increased from 2.77 ng/mL after a single dose to 13.1 ng/mL at steady-state after 2 weeks of once-a-day dosing (study Day 19), which is approximately 5-fold. Mean area under the plasma concentration time curve (AUC) from time 0 to 24 hours (AUC_{0-24}) of LDMP at steady-state was 3.01 times greater than the mean AUC extrapolated to infinity (AUC_{0-inf}) observed after a single dose indicating nonlinear kinetics.

The mean accumulation index, measured as the ratio of AUC_{0-24} on Day 19 to that on Day 1, was 9.71. The variability associated with total and peak exposures of paroxetine (as assessed by coefficient of variation %) exceeded 90% after single and multiple oral doses of LDMP. High interindividual variability in paroxetine concentrations and PK parameters was observed.

Table 7-1 Mean (CV%) paroxetine PK parameters by Day

PK Parameter (unit)	Day 1 (N=24)	Day 19 (N=24)
$AUC_{0\text{-}last}$ (hr*ng/mL)	86.95 (191.13)	237.34 (93.81)
$AUC_{0\text{-}inf}$ (hr*ng/mL)	78.80 (240.97)[a]	–
$AUC_{0\text{-}24}$ (hr*ng/mL)	38.90 (133.25)	237.28 (93.83)
C_{max} (ng/mL)	2.77 (122.20)	13.10 (91.03)
T_{max} (hr)[b]	6.00 (1.00, 8.00)	6.00 (3.00, 8.00)
k_{el} (hr^{-1})	0.05 (28.43)[a]	–
$t_{1/2}$ (hr)	17.30 (66.17)[a]	–
C_{min} (ng/mL)		7.67 (98.68)
$C_{avg,ss}$ (ng/mL)		9.89 (93.83)
Fluctuation index[c] (%)		75.76 (35.57, 153.20)
Accumulation index[c]		9.71 (0.12, 23.48)
$C_{\tau 18}$ (ng/mL)		8.53 (107.52)
$C_{\tau 19}$ (ng/mL)		8.35 (101.63)
$C_{\tau 20}$ (ng/mL)		8.79 (104.50)

[a]N=23; for patient 001-019, k_{el} and its associated parameters are not reported since the percent extrapolation of $AUC_{0\text{-}inf}$ was greater than 25%.
[b]Median (range) is presented for T_{max}.
[c]Mean (minimum, maximum) is presented for fluctuation index and accumulation index.
On Day 19, the 24-hour postdose sample for patient 001-013 was re-assayed. This 24-hour sample was excluded from PK parameter estimation in this table.
$AUC_{0\text{-}24}$=area under the serum concentration curve from time zero to 24 hours; $AUC_{0\text{-}last}$=area under the serum concentration curve from time zero to the last measurable concentration; $AUC_{0\text{-}inf}$=area under the plasma concentration versus time curve extrapolated to infinity; $C_{avg,ss}$=average plasma concentration during the dosing interval calculated as $AUC_{0\text{-}\tau}/\tau$, where τ = 24 hours; C_{max}=maximum observed serum concentration; C_{min}=minimum observed plasma concentration during the dosing interval (0 to 24 hours); C_{τ}=concentration at the end of dosing interval, concentration before dosing on Day 18 and Day 19, and concentration at 24 hours on Day 20; CV=coefficient of variation; k_{el}=elimination rate constant (slope of the natural log concentration versus time curve); PK=pharmacokinetic; T_{max}=time of the maximum observed serum concentration; $t_{1/2}$=elimination half-life.

Most subjects (23/24, 95.8%) experienced at least 1 treatment-emergent AE; however most AEs (67 events in 22/24 subjects, 91.7%) were mild, and the remainder of the AEs were moderate. Seventeen subjects experienced 33 AEs that were deemed possibly or probably related to LDMP. There were no serious AEs, and no clinically meaningful changes in laboratory values, vital signs, or electrocardiograms were observed.

In conclusion, upon multiple dosing, LDMP is well tolerated and exhibits nonlinear pharmacokinetics and extent of accumulation consistent with data in the published literature and data described in the Pexeva label.

Characterization of LDMP pharmacokinetics

The pharmacokinetic findings from LDMP 7.5 mg (Study N30-005) are in agreement with those in the published literature in which higher doses (20–50 mg) of paroxetine were used.

In a study of healthy men (N=25) who received 30 mg paroxetine mesylate tablets daily for 24 days, steady state was attained by Day 13 and nonlinear PK was observed (Pexeva PI). C_{max}, minimum observed plasma concentration (C_{min}), and $AUC_{0\text{-}24h}$ values were 7-, 10-, and 10-fold higher, respectively, than predicted values after a single dose. A similar nonlinear behavior was seen following multiple daily doses of 20 mg or 30 mg (Kaye et al 1989). The pharmacokinetics of paroxetine in elderly or young subjects with depression were similar to those in healthy subjects and displayed similar nonlinearity (Kaye et al 1989, Feng et al 2006). As a result of nonlinearity, a more than dose-proportional increase in paroxetine concentrations is also observed following increasing paroxetine doses. Sawamura et al showed that steady state mean plasma paroxetine concentration at 20 mg/day was approximately 5-fold higher than that at 10 mg/day, and at 40 mg/day it was approximately 4-fold higher than at 20 mg/day (Sawamura et al 2004).

Paroxetine undergoes a significant first-pass effect in the liver. As with several other SSRIs, paroxetine mesylate is metabolized by cytochrome P450 2D6 (CYP2D6); other isozymes, including cytochrome P450 3A4 (CYP3A4), also metabolize paroxetine but play a lesser role (Hiemke et al 2000, Jornil et al 2010, Preskorn 1997). Paroxetine is also a potent inhibitor of CYP2D6, displaying mechanism-based inhibition caused by irreversible binding of a paroxetine metabolite to the heme complex in the P450 enzyme (Jornil et al 2010, Alfaro et al 2000, Sindrup et al 1992a, Bertelsen et al 2003). The nonlinear pharmacokinetics observed with paroxetine mesylate reflects saturation of the CYP2D6 pathway (Pae et al 2010, Pexeva PI, Sindrup et al 1992a, Sindrup et al 1992b, Sawamura et al 2004).

Bioavailability data within the Pexeva NDA established the bioequivalence of paroxetine mesylate to paroxetine HCl (Paxil), and subsequent labeling reflects the absorption, distribution, metabolism, and elimination data from the label of its reference listed drug (RLD) Paxil. Furthermore, given the established paroxetine metabolic profile, and the clinically relevant inhibition of CYP2D6 occurring even at relatively low doses of paroxetine, the proposed LDMP label includes all DDI data from the Paxil label (Stout et al 2011, Skinner et al 2003, Stearns et al 2003b, Hemeryck et al 2000).

Regarding the use of LDMP in special populations, it should be noted that the Paxil label recommends starting with the low end of the dose range, the 10 mg dose. Considering that the paroxetine dose in LDMP is lower (7.5 mg) than the lowest dose of Paxil, no titration is necessary and information regarding titration is not relevant and is not included in the proposed LDMP label. As with higher doses of paroxetine mesylate (ie, 10, 20, 30, or 40 mg), coadministration of LDMP 7.5 mg with other drugs metabolized by CYP2D6 should be

approached with caution. The results from a published clinical drug interaction study between paroxetine and the CYP2D6 substrate tamoxifen, showed that the CYP2D6-mediated formation of the metabolite endoxifen decreased by 64% following the paroxetine dosing regimen of 10 mg/day for 4 weeks (Stearns et al 2003b). Consequently, women on tamoxifen should consider other options for the treatment of VMS.

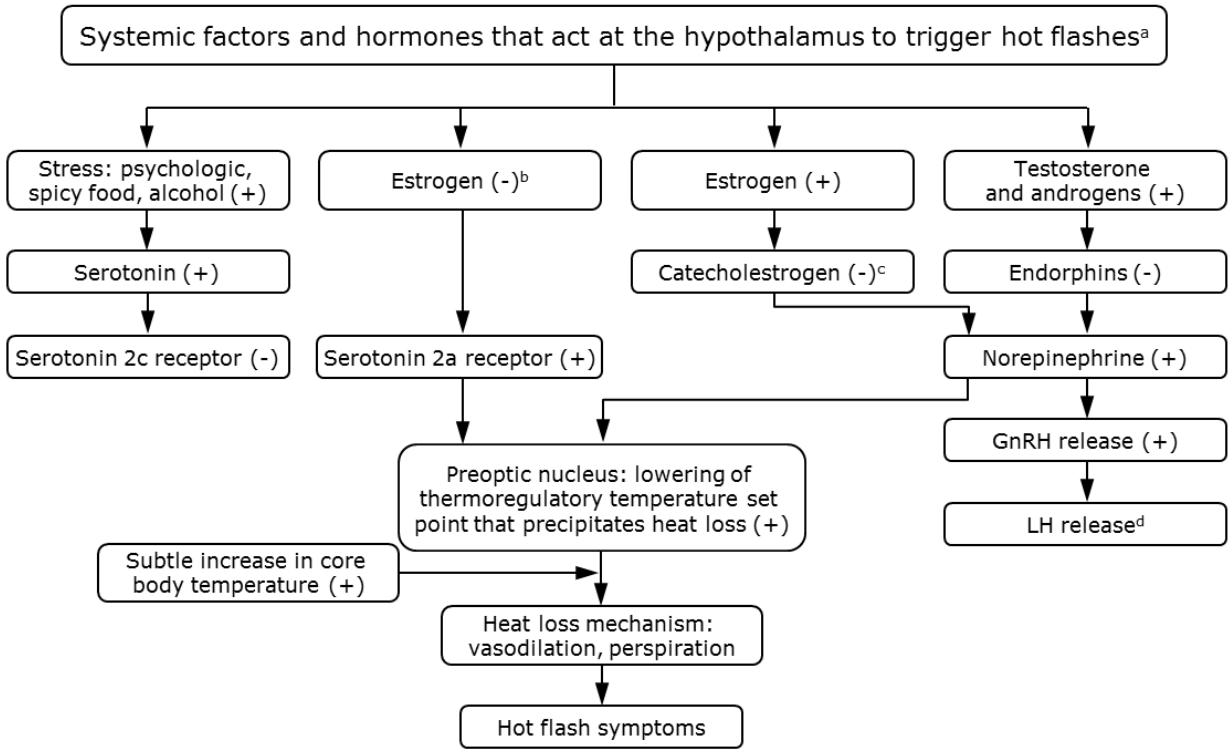
Pharmacology: Proposed mechanism of action and pharmacodynamics of LDMP

Nonclinical studies have shown that paroxetine mesylate is a potent and selective SSRI. Its mechanism of action for the treatment of VMS is thought to be related to the potentiation of neurotransmitters in the central nervous system that may help regulate body temperature (Bachmann 2005; Rossmanith and Ruebberdt 2009). The 7.5 mg dose of LDMP ensures its selectivity as an SSRI; at higher doses, paroxetine becomes less selective and may act as a dual serotonin/norepinephrine uptake inhibitor (Owens et al 2008).

Evidence from animal studies suggest that serotonin (5-HT) plays an important role in thermoregulation, and that the temperature increases associated with hot flashes could be linked to an overloading of serotonin receptor sites in the hypothalamus (Shanafelt et al 2002, Pachman et al 2010). Estrogen withdrawal during menopause is associated with decreasing levels of serotonin and an increase in serotonin receptors in the thermoregulatory nucleus, which is located in the hypothalamus and regulates core body temperature. In one model of the pathogenesis of hot flashes, estrogen withdrawal leads to a decrease in endorphin and catechol estrogen levels, enhancing the release of norepinephrine and serotonin. This lowers the set point in the thermoregulatory nucleus and triggers heat loss mechanisms such as hot flashes and sweating (**Figure 7-1**) (Shanafelt et al 2002, Pachman et al 2010).

The mechanism of action (MOA) of paroxetine in reducing hot flashes is different from its effects on mood and, while not fully elucidated, involves an effect on the thermoregulatory centers of the hypothalamus. Paroxetine acts within the hypothalamus to increase the amount of serotonin in the synaptic gap by inhibiting its reuptake, making more serotonin available. It has been postulated that increased serotonin levels activate the 5-HT2c receptors which results in the inhibition of 5-HT2a receptors, the latter of which, along with norepinephrine, lower the thermoregulatory set point in the hypothalamus. Inhibition of these receptors may restore the thermoregulatory set point to normal, removing the need for heat loss mechanisms (Berendsen 2000, Shanafelt et al 2002, Albertazzi 2006). Paroxetine is also thought to increase levels of brain-derived neurotrophic factor (BDNF) in postmenopausal women, which has been observed to improve climacteric symptoms (Cubeddu et al 2010).

Figure 7-1 Proposed model of pathways involved in hot flash symptoms



Reprinted from: Mayo Clinic Proceedings, 77(11). Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes, pages 1207-18, Copyright (2002), with permission from Elsevier.
[a](+) = Stimulates downstream signal; (–) = inhibits downstream signal.
[b]Estrogen acts to down-regulate serotonin 2a receptor concentration.
[c]Catechol estrogen inhibits tyrosine hydroxykinase metabolism of tyrosine to norepinephrine.
[d]Luteinizing hormone (LH) release occurs in the pituitary gland.
GnRH = gonadotropin-releasing hormone.

8 APPENDIX B: PROOF-OF-CONCEPT PHASE 2 STUDY N30-002 – DESIGN AND RESULTS

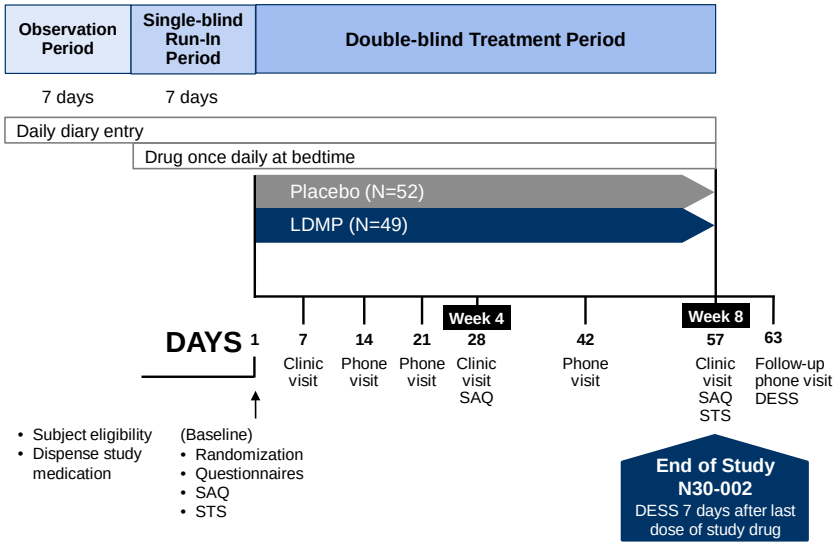
The Phase 2 N30-002 study provided proof of concept and showed that the 7.5 mg dose was well tolerated. In women with VMS associated with menopause, those treated with LDMP had larger decreases in the frequency and severity of moderate and severe hot flashes compared with placebo. This study also informed the estimation of effect size for the Phase 3 development program.

Study design and methods

The proof-of-concept Phase 2 N30-002 study was an 8-week, multicenter, double-blind, randomized study of LDMP versus placebo in patients with >7 moderate to severe hot flashes daily, or 50 moderate to severe hot flashes weekly, prior to randomization. The key exclusion criteria included history of hypersensitivity or adverse reaction to paroxetine, known nonresponse to previous SSRI or SNRI treatment for VMS, and presence of certain psychiatric disorders within specific time frames (eg, major depressive episode in past 2 weeks, generalized anxiety in past 6 months).

Following screening, patients entered a 1-week observation period followed by a 1-week single-blind run-in period of placebo treatment (patients were blind to treatment) to determine whether patients were capable of using the electronic diary properly and to reduce the number of placebo responders during the double-blind portion of the trial. Compliant patients who continued to meet the entry criteria for number of hot flashes with completed electronic diary entries were randomly assigned in a 1:1 ratio to receive LDMP 7.5 mg or placebo daily at bedtime for 8 weeks (**Figure 8-1**).

Figure 8-1 Phase 2 study design, N30-002



DESS=Discontinuation Emergent Signs and Symptoms Scale; SAQ= symptom assessment questionnaires including Arizona Sexual Experience scale and Numerical Rating Scale; STS=Suicidality Tracking Scale.

The primary endpoints were the mean change in weekly frequency and severity of moderate to severe VMS from baseline to Week 4 and from baseline to Week 8. The change in frequency in VMS was based on the number of moderate and severe hot flashes recorded in the patients' electronic daily diaries. VMS severity scores were calculated using the formula, $SS = (2 \cdot F_m + 3 \cdot F_s) \div (F_m + F_s)$, where SS is severity score, F_m is the frequency of moderate hot flashes, and F_s is the frequency of severe hot flashes.

Patient population

A total of 102 patients were randomized at 10 US sites and randomly assigned to receive LDMP or placebo. The mITT population included all consented and randomized patients who had valid diary data to calculate the average number of hot flashes per day for the run-in interval and for at least a single 7-day interval after initiating randomized treatment. Adequate diary data consisted of entries for at least 4 days in any 7-day interval. The mITT population comprised 101 patients (49 LDMP, 52 placebo); 1 patient assigned to the LDMP group was discontinued due to an AE that occurred before receiving study medication.

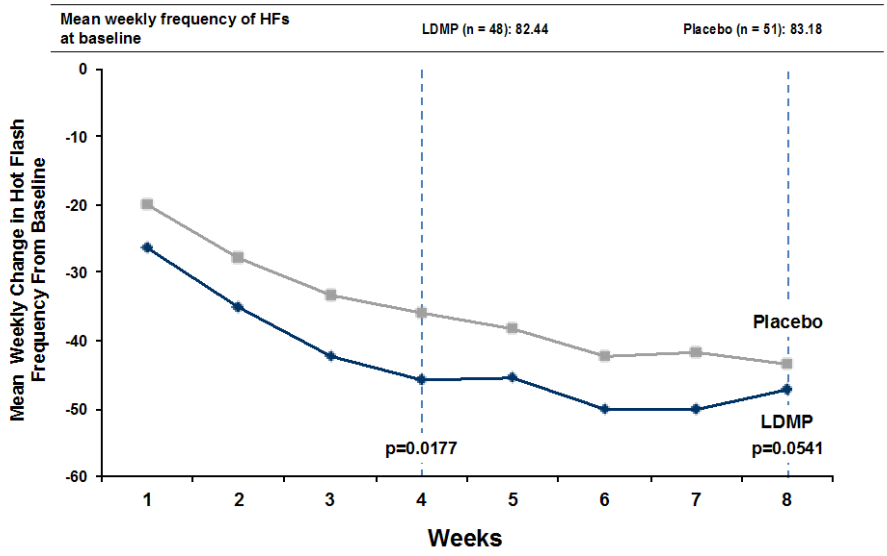
At baseline in the mITT population, the mean weekly frequency and the severity of hot flashes were similar in the two groups. The demographic characteristics of patients in the 2 treatment groups were also similar. The majority were White/Caucasian (71.4% LDMP, 69.2% placebo) or Black/African American (28.6% LDMP, 28.8% placebo). The median age was 56.0 years in patients treated with LDMP and 55.0 with placebo. Mean BMI was 27.59 kg/m^2 in patients treated with LDMP and 27.76 kg/m^2 with placebo.

Phase 2 efficacy results

Results of the Phase 2 study provided proof of concept for the use of 7.5 mg paroxetine mesylate in this setting and showed that the 7.5 mg dose was well tolerated. This study also informed the estimation of effect size for the Phase 3 development program demonstrating the safety and efficacy of LDMP for the treatment of moderate to severe VMS associated with menopause.

In the Phase 2 N30-002 study, LDMP 7.5 mg per day demonstrated efficacy in reducing the frequency and severity of moderate to severe VMS associated with menopause compared with placebo. The mean reduction in the frequency of moderate and severe VMS was significantly greater in patients treated with LDMP compared with placebo at Week 4 (-45.8 versus -35.9, respectively; p=0.0177). At Week 8, a larger numerical reduction was observed in patients treated with LDMP compared with placebo (-47.3 and -43.5, respectively; p=0.0541) **(Figure 8-2)**. Efficacy of LDMP as measured by mean change in frequency of moderate to severe hot flashes was evident as early as Week 1 (p=0.060) and was statistically significant by Week 2 (p=0.048).

Figure 8-2 Mean weekly change in hot flash frequency Week 1 through Week 8, mITT Population, Study N30-002



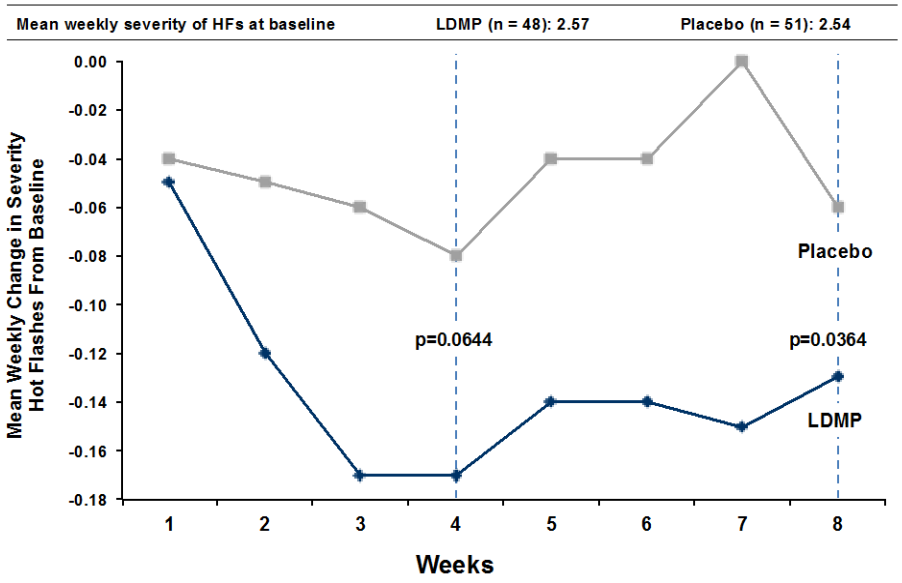
P values (based on mean values) are results of Generalized Equation Estimation (GEE) model with unity link function and the AR (1) covariance structure.
mITT=modified intent-to-treat.

Evaluation of the change in VMS severity showed that patients treated with LDMP had greater mean reduction in the severity of moderate and severe VMS compared with placebo at Week 4 (−0.171 and −0.078, respectively; p=0.0644). A statistically significant reduction with LDMP

compared with placebo was observed at Week 8 (−0.128 and −0.059, respectively; p=0.0364) (**Figure 8-3**).

Efficacy of LDMP compared with placebo as measured by hot flash composite score (frequency x severity) in Study N30-002 was evident as early as Week 2 (p=0.064); the difference between treatments in the hot flash composite score was statistically significant (p=0.036) by Week 3.

Figure 8-3 Mean weekly change in hot flash severity Week 1 through Week 8, mITT Population, Study N30-002



P values (based on mean values) are results of Generalized Equation Estimation (GEE) model with unity link function and the AR (1) covariance structure.
mITT=modified intent-to-treat.

9 APPENDIX C: DAILY HOT FLASH DIARY

Date week started: _ _ / _ _ / _ _ _ _ **Date week ended**: _ _ / _ _ / _ _ _ _

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Number of today's hot flashes that were mild, moderate or severe	__ mild __ moderate __ severe	__ mild __ moderate __ severe	__ mild __ moderate __ severe	__ mild __ moderate __ severe	__ mild __ moderate __ severe	__ mild __ moderate __ severe	__ mild __ moderate __ severe
Total number of moderate to severe hot flashes							
Total number of hot flashes							

10 APPENDIX D: MISSING DATA

The Phase 3 studies reported here are longitudinal by nature with the main prespecified assessments at predetermined time points; the nearly inevitable existence of missing data is always a concern. Missing data prevents analysis under the ITT principle and therefore it is important to evaluate whether the existence of missing data is a major factor.

In general, the outcome data from the diary are computed as weekly measures and then may be rescaled to daily values in order to maintain compatibility with precedent work in VMS. There are two general classes of missing diary data in these studies: daily diary entries and weekly data. The procedures used to "fill-in" missed daily entries in order to compute weekly diary data measures can still result in a missing weekly assessment. Outcome measures that are assessed at specific study visits can be missed or a patient can leave the study, thereby missing all subsequent assessments.

The main analyses presented are on available data with no imputation (with the exception of the diary fill-in procedures previously described). The primary prespecified method for assessing the impact of missing data was the LOCF method. Two other methods also provide insight into the impact of missing data: (1) the Mixed Model Repeated Measure (MMRM) using an analysis set consistent with the ITT principle has been used selectively, dependent on the nature of the outcome measure; (2) selective outcomes were dichotomized into "response" versus "no response" and subsequently analyses were done with missing outcomes imputed as "no response," thereby enabling an analysis in the spirit of ITT analysis. The imputation used in the latter case is based on the assumption that missing data are generally associated with "no response," and the impact of this assumption is illustrated in selected cases where statistical significance is an issue by using a tipping point analysis. In a tipping point analysis, all possible reversals of the imputed observations are explored in order to assess how far the original imputation is from the border where defining statistical significance reverses.

The quantity of missing data at each weekly visit is shown in **Tables 10-1** and **10-2** for Studies N30-003 and N30-004 for the co-primary endpoint of hot flash frequency. The 12-week missing data outcome are highlighted in gray to emphasize that the studies differ in duration.

Table 10-1 Missing data at each weekly visit for the primary change in frequency variable, Study N30-003

Week	Placebo n (%)	Placebo Missing Data[a] n	Placebo Last Visit[b] n	LDMP n (%)	LDMP Missing Data[a] n	LDMP Last Visit[b] n
0	305 (100.0)	0	0	301 (100.0)	0	0
1	305 (100.0)	0	4	301 (100.0)	0	5
2	301 (98.7)	4	3	296 (98.3)	5	4
3	298 (97.7)	7	4	292 (97.0)	9	3
4	294 (96.4)	12	5	289 (96.0)	12	1
5	289 (94.8)	16	2	288 (95.7)	13	7
6	287 (94.1)	19	2	281 (93.4)	20	1
7	285 (93.4)	20	2	280 (93.0)	24	1
8	283 (92.8)	22	2	279 (92.7)	24	3
9	281 (92.1)	25	2	276 (91.7)	26	1
10	279 (91.5)	27	0	275 (91.4)	28	5
11	279 (91.5)	29	5	270 (89.7)	33	6
12	274 (89.8)	31	274	264 (87.7)	37	264

[a]The number of cases with no data available in the analysis for the target variable at that visit, including patients with incidentally missing data and patients who had previously had their last visit.
[b]The number of patients having their last visit at that visit.

Table 10-2 Missing data at each weekly visit for the primary change in frequency variable, Study N30-004

Week	Placebo n (%)	Placebo Missing data[a] n	Placebo Last visit[b] n	LDMP n (%)	LDMP Missing data[a] n	LDMP Last visit[b] n
0	284 (100.0)	0	0	284 (100.0)	0	0
1	284 (100.0)	0	2	284 (100.0)	0	4
2	282 (99.3)	2	3	280 (98.6)	5	2
3	279 (98.2)	5	5	278 (97.9)	6	2
4	274 (96.5)	10	7	276 (97.2)	8	4
5	267 (94.0)	17	6	272 (95.8)	13	4
6	261 (91.9)	23	5	268 (94.4)	16	2
7	256 (90.1)	28	2	266 (93.7)	19	3
8	254 (89.4)	30	2	263 (92.6)	22	1
9	252 (88.7)	32	0	262 (92.3)	24	1
10	252 (88.7)	32	1	261 (91.9)	26	2
11	251 (88.4)	34	5	259 (91.2)	26	2
12	246 (86.6)	40	6	257 (90.5)	27	7
13	240 (84.5)	45	7	250 (88.0)	37	2
14	233 (82.0)	52	1	248 (87.3)	36	0
15	232 (81.7)	53	1	248 (87.3)	36	2
16	231 (81.3)	53	3	246 (86.6)	40	2
17	228 (80.3)	57	2	244 (85.9)	40	3
18	226 (79.6)	60	4	241 (84.9)	48	1
19	222 (78.2)	65	0	240 (84.5)	48	1
20	222 (78.2)	64	2	239 (84.2)	50	0
21	220 (77.5)	66	0	239 (84.2)	49	2
22	220 (77.5)	65	2	237 (83.5)	50	1
23	218 (76.8)	66	3	236 (83.1)	51	2
24	215 (75.7)	69	215	234 (82.4)	50	234

[a]The number of cases with no data available in the analysis for the target variable at that visit, including patients with incidentally missing data and patients who had previously had their last visit.
[b]The number of patients having their last visit at that visit.

These tables show that the amount of missing data is not large. For example, at Week 12 the percent of patients available in the analysis set at that visit ranges from 86.6% (placebo arm of Study N30-004) to 90.5% (LDMP arm of Study N30-004). There does not seem to be a trend with respect to missing data by arm. For example, at Week 12 in Study N30-003, the LDMP arm had more missing data, whereas at Week 12 in Study N30-004, the placebo arm had more missing data.

In general, the evaluations of the impact of missing data on the results found no change in general conclusions compared with analyses using all available data.

11 APPENDIX E: EXPLORATORY ANALYSES TO ASSESS EFFECTS ON SEVERITY

Severity score

Noven conducted several exploratory analyses to assess LDMP effects on VMS severity and to provide perspective on the results of the primary analysis.

The first exploratory analysis used the weighted average severity score but included mild hot flashes also in the equation. This method was previously used in HT clinical trials for moderate to severe VMS.

Mean weekly and daily hot flash severity score with mild, moderate and severe hot flashes

The hot flash severity score for each patient was defined as $(1 \cdot F_{mild} + 2 \cdot F_m + 3 \cdot F_s) \div (F_{mild} + F_m + F_s)$; F_{mild} = number of mild hot flashes; F_m = number of moderate hot flashes and F_s = number of severe hot flashes. These scores were used to evaluate the change from baseline to Week 4 and Week 12 in the severity of moderate to severe VMS per week and are shown in **Table 11-1** and **Figure 11-1**.

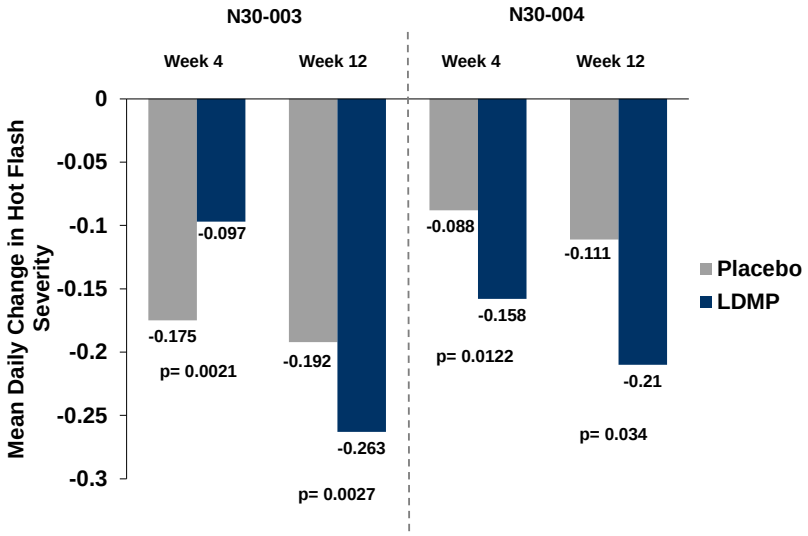
Table 11-1 Results for severity co-primary endpoints using mild, moderate, and severe hot flashes, mITT population, Studies N30-003 and N30-004

	Week 4			Week 12		
	Change from Baseline			Change from Baseline		
	Placebo	LDMP	P value	Placebo	LDMP	P value
Study N30-003						
Reduction in daily hot flash severity (mean), ranked ANCOVA	n = 293 -0.175 ± 0.04	n = 289 -0.097 ± 0.35	0.0021	n = 266 -0.192 ± 0.49	n = 256 -0.263 ± 0.52	0.0227
Reduction in weekly hot flash severity (mean), ranked ANCOVA	n = 289 -0.097 ± 0.34	n = 289 -0.171 ± 0.40	0.0026	n = 256 -0.193 ± 0.48	n = 266 -0.261 ± 0.52	0.0314
Study N30-004						
Reduction in daily hot flash severity (mean), ranked ANCOVA	n = 274 -0.088 ± 0.30	n = 275 -0.158 ± 0.37	0.0122	n = 241 -0.0.111 ± 0.40	n = 254 -0.210 ± 0.46	0.0340
Reduction in weekly hot flash severity (mean), ranked ANCOVA	n = 274 -0.086 ± 0.29	n = 275 -0.153 ± 0.37	0.0222	n = 254 -0.110 ± 0.40	n = 254 -0.204 ± 0.46	0.0053

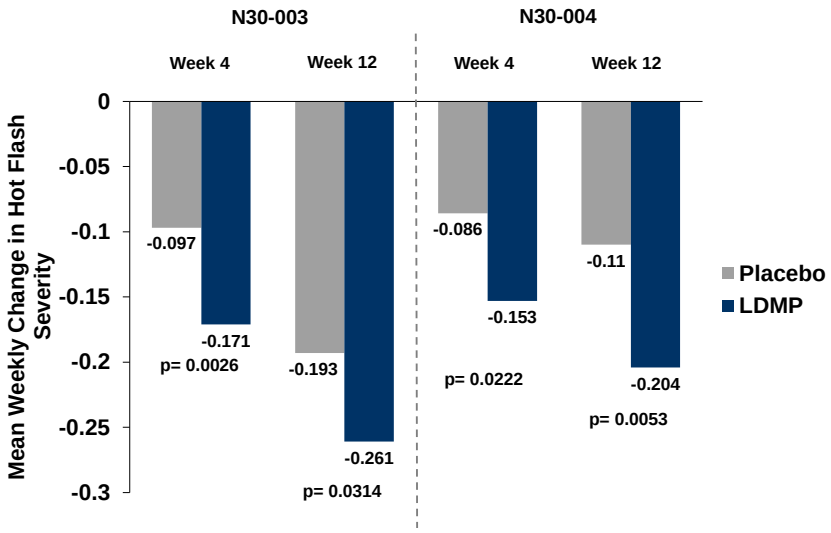
ANCOVA=analysis of covariance; mITT=modified intent-to-treat.

Figure 11-1 Mean daily and weekly changes in severity of mild, moderate, and severe hot flashes, mITT Population, Phase 3 Studies

Daily



Weekly



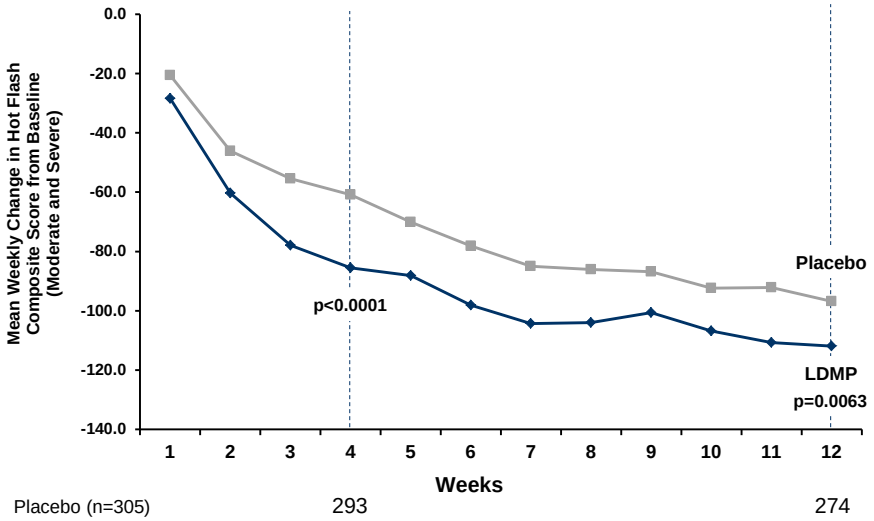
P values are results of rank transformed ANCOVA.
mITT=modified intent-to-treat.

The second exploratory analysis examined the severity by looking at the weighted composite score, without averaging by the total number of hot flashes. A composite score has been used as a reliable measure of changes in hot flash frequency/severity in other clinical studies of nonhormonal treatments for VMS associated with menopause (Archer et al 2009a, Archer et al 2009b, Stearns et al 2003a, Sloan et al 2001). Composite scores are clinically meaningful and

reflect a patient's combined burden of hot flash frequency and severity, as patients do not experience hot flash frequency or severity separately.

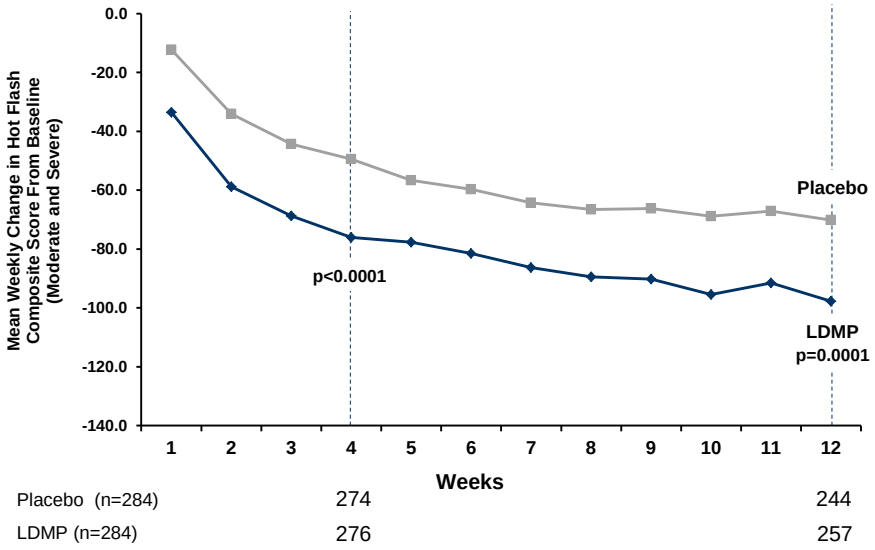
In Study N30-003, results for mean composite score changes in patients treated with LDMP versus placebo at Week 4 (−85.51 versus −60.68, respectively) and Week 12 (−111.9 versus −96.85) and at all other weekly assessments ($p \leq 0.0074$) were significantly greater in patients treated with LDMP compared with placebo (**Figure 11-2)**. In Study N30-004, significantly greater changes in composite score with LDMP were also shown at Week 4 (−76.08 versus −49.50) and Week 12 (−97.73 versus −70.20) and all other weekly assessments ($p \leq 0.001$) compared with placebo (**Figure 11-3**).

Figure 11-2 Mean weekly change in moderate and severe hot flash composite score Week 1 through Week 12, N30-003



P values (based on median values) are results of rank transformed ANCOVA.
mITT=modified intent-to-treat.

Figure 11-3 Mean weekly change in moderate and severe hot flash composite score Week 1 through Week 12, N30-004



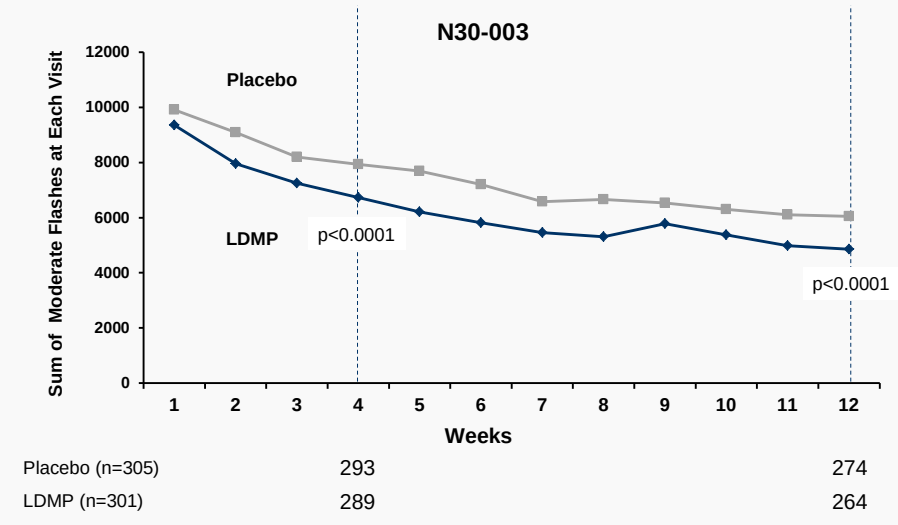
P values are results of rank transformed ANCOVA.
mITT=modified intent-to-treat.

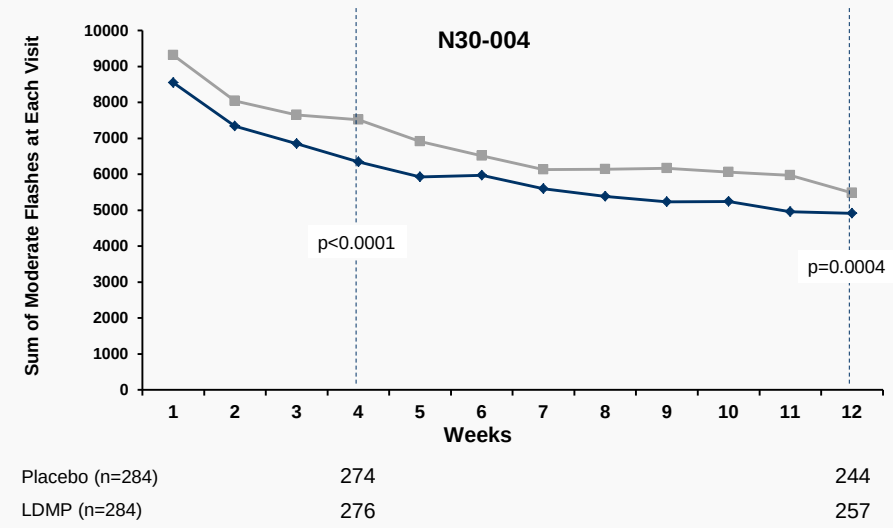
In a third exploratory analysis, the mean weekly reduction in total number of hot flashes was analyzed separately for moderate and severe hot flashes. Patients treated with LDMP had statistically significant reductions in the total number of severe only and moderate only hot flashes compared with placebo at almost every weekly time point in both Phase 3 studies.

Sum of moderate hot flashes and severe hot flashes

The reduction in number of moderate only hot flashes was significantly greater with LDMP compared with placebo at Weeks 4 and 12 in Studies N30-003 and N30-004 (**Figure 11-4**).

Figure 11-4 Mean weekly sum of only moderate hot flashes Week 1 through Week 12, mITT Population, N30-003 and N30-004

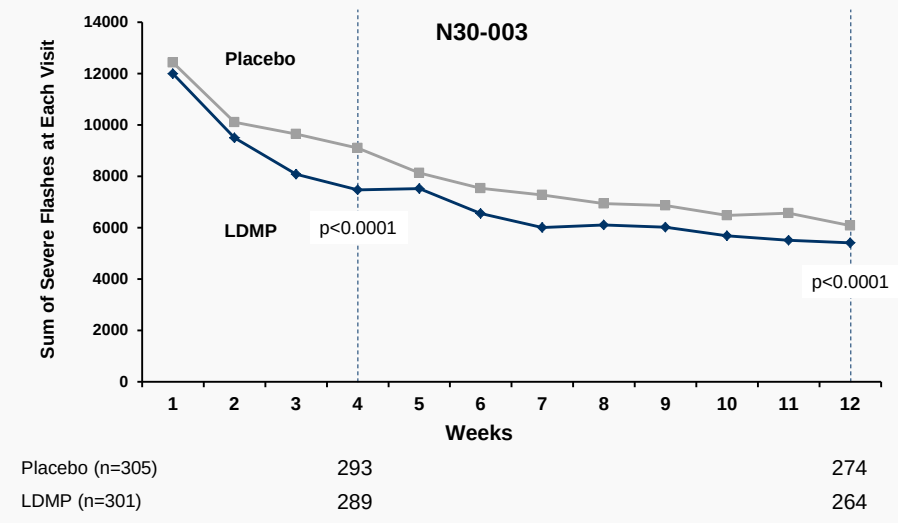


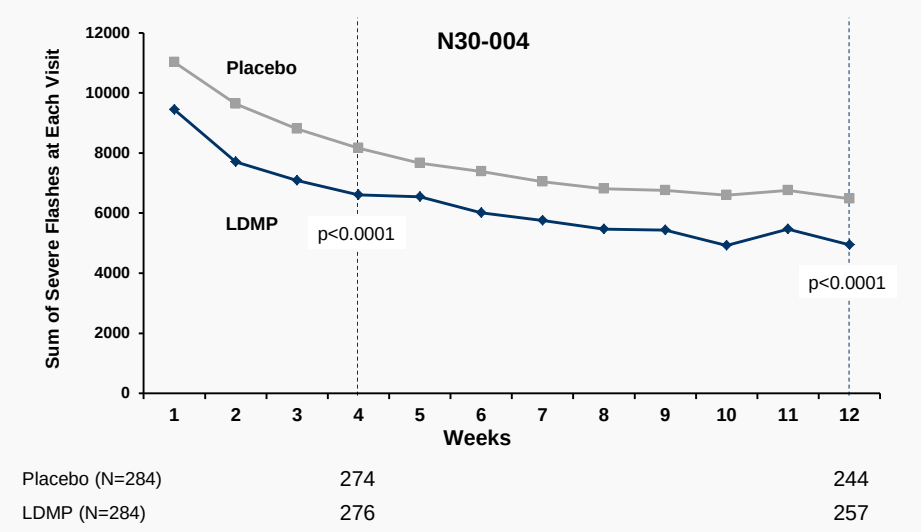


P values are results of rank chi-square test.
mITT=modified intent-to-treat.

Likewise, patients treated with LDMP had statistically significant reductions in the total number of severe only hot flashes versus placebo from Week 2 through 12 in Study N30-003 and Week 1 through 12 in Study N30-004 (**Figure 11-5**).

Figure 11-5 Mean weekly sum of only severe hot flashes Week 1 through Week 12, mITT Population, N30-003 and N30-004





P values are results of rank chi-square test.
mITT=modified intent-to-treat.

12 APPENDIX F: N30-003, 12-WEEK STUDY: CO-PRIMARY, SUPPORTIVE AND SECONDARY ENDPOINTS, MITT POPULATION

	Week 4			Week 12		
	Change from Baseline			Change from Baseline		
Endpoint	**Placebo**	**LDMP**	**P value**	**Placebo**	**LDMP**	**P value**
Co-primary endpoints						
Daily frequency, rank transformed ANCOVA, median	n = 293 -3.14	n = 289 -4.29	<0.0001	n = 274 -5.00	n = 264 -5.93	0.0090
Daily frequency, LOCF, median	n = 305 -3.14	n = 301 -4.29	<0.0001	n = 305 -5.00	n = 301 -5.86	0.0038
Daily severity, rank transformed ANCOVA, median	n = 289 0.000	n = 281 -0.052	0.0017	n = 253 -0.018	n = 236 -0.058	0.1658
Daily severity, LOCF, median	n = 305 0.000	n = 301 -0.047	0.0008	n = 305 -0.017	n = 301 -0.060	0.0728
Supportive Endpoint						
Clinical meaningfulness anchored to PGI-I (%)	47	58	0.0058	42	48	0.1332
Secondary Endpoints						
Nighttime awakenings, median	n = 288 -7.12	n = 289 -8.33	0.0013	n = 270 -11.05	n = 264 -12.00	0.0277
Frequency BMI <32 kg/m^2, median	n = 206 -23.00	n = 211 -42.00	0.0001	n = 196 -35.00	n = 193 -46.00	0.0034
Frequency BMI ≥32 kg/m^2, median	n = 87 -19.00	n = 77 -28.00	0.1029	n = 78 -37.50	n = 70 -35.00	0.6952
Severity BMI <32 kg/m^2, median	n = 203 0.00	n = 206 -0.055	0.0042	n = 179 -0.010	n = 170 -0.043	0.1491
Severity BMI ≥32 kg/m^2, median	n = 86 -0.014	n = 74 -0.023	0.4576	n = 74 -0.030	n = 65 -0.079	0.7793
GCS total score, median	n = 282 -2.00	n = 280 -3.00	0.0868	n = 265 -3.00	n = 265 -4.00	0.0211
≥50% reduction in frequency (%)	n = 305 29.18	n = 301 40.20	0.0045	n = 305 44.92	n = 301 49.83	0.2258

	Week 4			Week 12		
	Change from Baseline			Change from Baseline		
Endpoint	**Placebo**	**LDMP**	**P value**	**Placebo**	**LDMP**	**P value**
PGI responder, (%)	61.75	68.21	0.1080	64.60	72.82	0.0336
NRS daytime and nighttime responders (%)	n = 302 30.46	n = 300 39.00	0.0085	n = 304 45.72	n = 301 46.51	0.5483
ASEX total score, median	n = 282 0.00	n = 280 0.00	0.5538	n = 265 -1.00	n = 265 0.00	0.3024
HFRDIS (more interference) (%)	n = 275 32.00	n = 278 26.98	0.0706	n = 246 21.95	n = 244 19.67	0.5839
CGI responders, (%)	n =285 57.89	n = 280 68.93	0.0067	n = 291 63.92	n =288 71.88	0.0407
HADS – Abnormal anxiety and depression (%)	n = 281 3.56	n = 281 3.56	0.7350	n = 255 2.75	n = 248 2.02	0.7866
POMS (more disturbance) (%)	n = 280 41.79	n = 280 32.50	0.0671	n = 254 46.06	n = 246 33.74	0.0170
BMI kg/m^2, median	n = 288 0.04	n = 282 0.00	0.0497	n = 295 0.17	n = 290 0.00	0.0849

ANCOVA=analysis of covariance; ASEX=Arizona Sexual Experience Scale; BMI=body mass index; GCS=Greene Climacteric Scale; HADS=Hospital Anxiety and Depression Scale; HFRDIS=Hot Flash Related Diary interference Scale; LOCF=last observation carried forward; mITT=modified intent-to-treat; NRS=Numerical rating Scale; PGI=Patient Global Improvement; POMS=Profile of Moods State.

13 APPENDIX G: N30-004, 24-WEEK STUDY: CO-PRIMARY, SUPPORTIVE AND SECONDARY ENDPOINTS, MITT POPULATION

	Week 4			Week 12			Week 24		
	Change from Baseline			Change from Baseline			Change from Baseline		
Endpoint	**Placebo**	**LDMP**	**P value**	**Placebo**	**LDMP**	**P value**	**Placebo**	**LDMP**	**P value**
Co-primary endpoints									
Daily frequency, rank transformed ANCOVA, median	n = 274 -2.500	n = 276 -3.786	<0.0001	n = 244 -3.857	n = 257 -5.571	0.0001	n = 215 -4.571	n = 234 -5.857	0.0021
Daily frequency, LOCF, median	n = 284 -2.500	n = 284 -3.714	<0.0001	n = 284 -3.357	n = 284 -5.214	<0.0001	n = 284 -4.036	n = 284 -5.429	0.0002
Daily severity, rank transformed ANCOVA, median	n = 271 -0.008	n = 268 -0.040	0.0368	n = 236 0.000	n = 245 -0.051	0.0064	n = 201 -0.015	n = 213 -0.085	0.0320
Daily severity, LOCF, median	n = 284 -0.008	n = 284 -0.040	0.0084	n = 284 0.000	n = 284 -0.062	0.0020	n = 284 -0.015	n = 284 -0.084	0.0057
Supportive Endpoint									
Persistence of benefit (%)							n = 284 36.27	n = 284 47.54	0.0066
Secondary Endpoints									
Nighttime awakenings, median	n = 269 -6.62	n = 273 -8.50	0.0104	n = 241 -8.67	n = 255 -13.15	<0.0001	n = 214 -10.54	n = 232 -14.56	<0.0001
Frequency BMI <32 kg/m^2, median	n = 205 -18.0	n = 212 -28.50	0.0005	n = 179 -27.0	n = 197 -41.0	0.0004	n = 156 -30.50	n = 180 -42.00	0.0030
Frequency BMI ≥32 kg/m^2, median	n = 69 -17.0	n = 64 -22.00	0.0218	n = 65 -23.0	n = 60 -31.5	0.1698	n = 59 -35.00	n = 54 -36.50	0.3142
Severity BMI <32 kg/m^2, median	n = 204 -0.004	n = 205 -0.033	0.0554	n = 173 -0.00	n = 187 -0.045	0.0070	n = 144 -0.004	n = 162 -0.084	0.0144
Severity BMI ≥32 kg/m^2, median	n = 67 -0.036	n = 63 -0.039	0.4945	n = 63 -0.051	n = 58 -0.052	0.6577	n = 57 -0.060	n = 51 -0.068	0.8044
GCS total score, median	n = 238 -3.00	n = 244 -3.00	0.4589	n = 203 -3.00	n = 216 -4.00	0.0180	n = 186 -3.00	n = 210 -4.00	0.8645

	Week 4			Week 12			Week 24		
	Change from Baseline			Change from Baseline			Change from Baseline		
Endpoint	**Placebo**	**LDMP**	**P value**	**Placebo**	**LDMP**	**P value**	**Placebo**	**LDMP**	**P value**
≥50% reduction in frequency (%)	n = 284 25.35	n = 284 35.56	0.0084	n = 284 33.80	n = 284 49.30	0.0002	n = 284 36.27	n = 284 47.54	0.0066
NRS daytime and nighttime responders, (%)	n = 277 25.27	n = 279 35.48	0.0191	n = 281 37.72	n = 281 46.62	0.0427	n = 281 39.15	n = 284 54.58	0.0005
ASEX total score, median	n = 237 0.00	n = 242 0.00	0.7024	n = 202 0.00	n = 216 0.00	0.9279	n = 185 0.00	n = 210 0.00	0.8553
HFRDIS (more interference) (%)	n = 236 30.51	n = 242 26.03	0.4113	n = 197 21.32	n = 214 15.89	0.1695	n = 181 21.55	n = 199 19.60	0.8858
CGI responders, (%)	n = 265 53.58	n = 274 67.88	0.0007	n = 231 59.74	n = 249 69.88	0.0203	n = 268 58.21	n = 269 73.23	0.0003
HADS – Abnormal anxiety and depression (%)	n = 246 2.44	n = 248 5.65	0.0557	n = 210 5.24	n = 218 4.13	0.4635	n = 192 2.60	n = 205 4.39	0.4714
POMS (more disturbance) (%)	n = 243 42.39	n = 246 37.40	0.1756	n = 208 44.23	n = 218 37.16	0.3128	n = 193 40.41	n = 205 40.98	0.6611
BMI kg/m^2, median	n = 263 0.08	n = 272 0.00	0.0015	n = 233 0.11	n = 250 0.15	0.7313	n = 268 0.16	n = 270 0.02	0.3173

ANCOVA=analysis of covariance; ASEX=Arizona Sexual Experience Scale; BMI=body mass index; GCS=Greene Climacteric Scale; HADS=Hospital Anxiety and Depression Scale; LOCF=last observation carried forward; mITT=modified intent-to-treat; NRS=Numerical rating Scale; PGI=Patient Global Improvement.

14 APPENDIX H: DAILY SLEEP DIARY

Please complete this sleep diary EACH morning between 6 A.M. and 11 A.M.

1. Did you fall asleep last night?(circle) **YES** **NO**

2. How long did it take you to fall asleep last night? (Hours/Minutes) _____

3. Last night, how many times did you wake up due to a hot flash? _____

4. How long did you sleep last night? (Hours/Minutes) _____

15 APPENDIX I: THE GREENE CLIMACTERIC SCALE

SEVERITY OF PROBLEM IS SCORED AS FOLLOWS:

SCORE
0.....None
1.....Mild
2.....Moderate
3.....Severe

Heart beating quickly and strongly	0	1	2	3
Feeling tense or nervous	0	1	2	3
Difficulty in sleeping	0	1	2	3
Excitable	0	1	2	3
Attacks of panic	0	1	2	3
Difficulty in concentrating	0	1	2	3
Feeling tired or lacking in energy	0	1	2	3
Loss of interest in most things	0	1	2	3
Feeling unhappy or depressed	0	1	2	3
Crying spells	0	1	2	3
Irritability	0	1	2	3

Feeling dizzy or faint	0	1	2	3
Pressure or tightness in head or body	0	1	2	3
Parts of body feeling numb or tingling	0	1	2	3
Headaches	0	1	2	3
Muscle or joint pains	0	1	2	3
Loss of feeling in hands or feet	0	1	2	3
Breathing difficulties	0	1	2	3
Hot flushes	0	1	2	3
Sweating at night	0	1	2	3
Loss of interest in sex	0	1	2	3

16 APPENDIX J: HOT FLASH RELATED DAILY INTERFERENCE SCALE

Please circle one number to the right of each phrase to describe how much DURING THE PAST WEEK hot flashes have INTERFERED with each aspect of your life. Higher numbers indicate more interference with your life. If you are not experiencing hot flashes or if hot flashes do not interfere with these aspects of your life, please mark zero to the right of each question.

	Do not interfere										**Completely Interfere**
1. Work (work outside the home and housework)	0	1	2	3	4	5	6	7	8	9	10
2. Social activities (time spent with family, friends, etc.)	0	1	2	3	4	5	6	7	8	9	10
3. Leisure activities (time relaxing, doing hobbies, etc.)	0	1	2	3	4	5	6	7	8	9	10
4. Sleep	0	1	2	3	4	5	6	7	8	9	10
5. Mood	0	1	2	3	4	5	6	7	8	9	10
6. Concentration	0	1	2	3	4	5	6	7	8	9	10
7. Relations with others	0	1	2	3	4	5	6	7	8	9	10
8. Sexuality	0	1	2	3	4	5	6	7	8	9	10
9. Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10
10. Overall quality of life	0	1	2	3	4	5	6	7	8	9	10

17 APPENDIX K: PATIENT SATISFACTION QUESTIONNAIRE

Are you satisfied with your treatment?

☐Yes

☐No

18 APPENDIX L: PATIENT GLOBAL IMPRESSION OF IMPROVEMENT

Compared to before starting study medication, how would you describe your hot flushes now?

0 = Not assessed

1 = Very much better

2 = Much better

3 = A little better

4 = No change

5 = A little worse

6 = Much worse

7 = Very much worse

19 APPENDIX M: CLINICAL GLOBAL IMPRESSION

Severity of Illness

Considering your total clinical experience with this particular population, how ill has the patient been over the past week? (Circle one)

Rating should account for severity of the patient's VMS.

0 = Not assessed
1 = Normal, not at all ill
2 = Borderline ill
3 = Mildly ill
4 = Moderately ill
5 = Markedly ill
6 = Severely ill
7 = Extremely ill

Global Improvement

Compared to the patient's condition at the beginning of this study, how much has the patient's illness improved or worsened? (Circle one)

Rating should account for severity of the patient's VMS.

0 = Not assessed
1 = Very much improved
2 = Much improved
3 = Minimally improved
4 = No change
5 = Minimally worse
6 = Much worse
7 = Very much worse

20 APPENDIX N: NUMERICAL RATING SCALE

In the past one week how bothered were you by your daytime hot flashes?

Not bothered at all										Very much bothered
0	1	2	3	4	5	6	7	8	9	10

In the past one week how bothered were you by your nighttime hot flashes?

Not bothered at all										Very much bothered
0	1	2	3	4	5	6	7	8	9	10

21 APPENDIX O: ARIZONA SEXUAL EXPERIENCE SCALE

1. How strong is your sex drive?

1 Extremely strong
2 Very strong
3 Somewhat strong
4 Somewhat weak
5 Very weak
6 Absent

☐

2. How easily are you sexually aroused?

1 Extremely easily
2 Very easily
3 Somewhat easily
4 Somewhat difficult
5 Very difficult
6 Never

☐

3a . Can you easily get and keep an erection?

1 Extremely easily
2 Very easily
3 Somewhat easily
4 Somewhat difficult
5 Very difficult
6 Never

☐

3b. How easily does your vagina become moist?

1 Extremely easily
2 Very easily
3 Somewhat easily
4 Somewhat difficult
5 Very difficult
6 Never

☐

4. How easily can you reach orgasm?

1 Extremely easily
2 Very easily
3 Somewhat easily
4 Somewhat difficult
5 Very difficult
6 Never

☐

5. Are your orgasms satisfying?

1 Extremely satisfying
2 Very satisfying
3 Somewhat satisfying
4 Somewhat unsatisfying
5 Extremely unsatisfying
6 Never achieve orgasm

☐

Total Score ☐

22 APPENDIX P: HOSPITAL ANXIETY AND DEPRESSION SCALE

I feel tense or 'wound up':	**A**	**I feel as if I am slowed down:**	**D**
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0

I still enjoy the things I used to enjoy:	**D**	**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**	**I have lost interest in my appearance:**	**D**
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**	**I feel restless as if I have to be on the move:**	**A**
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0

Worrying thoughts go through my mind:	**A**	**I look forward with enjoyment to things:**	**D**
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2

I feel cheerful:	**D**	**I get sudden feelings of panic:**	**A**
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0

I can sit at ease and feel relaxed:	**A**	**I can enjoy a good book or radio or TV program:**	**D**
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

23 APPENDIX Q: PROFILE OF MOOD STATES

Profile of Mood States

Subject's Initials _____

Birth date _____

Date _____

Subject Code No. _____

Directions: Describe HOW YOU FEEL RIGHT NOW by checking one space after each of the words listed below:

FEELING	Not at all	A little	Mod.	Quite a bit	Extremely
Friendly	1	2	3	4	5
Tense	1	2	3	4	5
Angry	1	2	3	4	5
Worn Out	1	2	3	4	5
Unhappy	1	2	3	4	5
Clear-headed	1	2	3	4	5
Lively	1	2	3	4	5
Confused	1	2	3	4	5
Sorry for things done	1	2	3	4	5
Shaky	1	2	3	4	5
Listless	1	2	3	4	5
Peeved	1	2	3	4	5
Considerate	1	2	3	4	5
Sad	1	2	3	4	5
Active	1	2	3	4	5
On edge	1	2	3	4	5
Grouchy	1	2	3	4	5
Blue	1	2	3	4	5
Energetic	1	2	3	4	5
Panicky	1	2	3	4	5
Hopeless	1	2	3	4	5
Relaxed	1	2	3	4	5
Unworthy	1	2	3	4	5
Spiteful	1	2	3	4	5
Sympathetic	1	2	3	4	5
Uneasy	1	2	3	4	5
Restless	1	2	3	4	5

Unable to concentrate	1	2	3	4	5
Fatigued	1	2	3	4	5
Helpful	1	2	3	4	5
Annoyed	1	2	3	4	5
Discouraged	1	2	3	4	5
Resentful	1	2	3	4	5
Nervous	1	2	3	4	5
Lonely	1	2	3	4	5
Miserable	1	2	3	4	5
Muddled	1	2	3	4	5
Cheerful	1	2	3	4	5
Bitter	1	2	3	4	5
Exhausted	1	2	3	4	5
Anxious	1	2	3	4	5
Ready to fight	1	2	3	4	5
Good-natured	1	2	3	4	5
Gloomy	1	2	3	4	5
Desperate	1	2	3	4	5
Sluggish	1	2	3	4	5
Rebellious	1	2	3	4	5
Helpless	1	2	3	4	5
Weary	1	2	3	4	5
Bewildered	1	2	3	4	5
Alert	1	2	3	4	5
Deceived	1	2	3	4	5
Furious	1	2	3	4	5
Effacious	1	2	3	4	5
Trusting	1	2	3	4	5
Full of pep	1	2	3	4	5
Bad-tempered	1	2	3	4	5
Worthless	1	2	3	4	5
Forgetful	1	2	3	4	5
Carefree	1	2	3	4	5
Terrified	1	2	3	4	5
Guilty	1	2	3	4	5
Vigorous	1	2	3	4	5
Uncertain about things	1	2	3	4	5
Bushed	1	2	3	4	5

24 APPENDIX R: SUICIDALITY TRACKING SCALE (STS)

SUICIDALITY TRACKING SCALE

(From MINI Tracking, Module C. Copyright Sheehan et al 2005 revision)

RATING INSTRUCTIONS:

THE CLINICIAN SHOULD ENSURE THAT ALL DIMENSIONS OF THE QUESTION ARE TAKEN INTO ACCOUNT IN CHOOSING THE APPROPRIATE RESPONSE (FOR EXAMPLE, TIME FRAME, FREQUENCY AND SEVERITY)

1. **Over the past week did you suffer any accident?**	NO	YES				
IF NO, SKIP TO QUESTION 2: IF YES, ASK:						
	not at all	a little	moderately	markedly	extremely	
1a. to what extent did you plan or intend to hurt yourself in that accident (either passively or actively)?	0	1	2	3	4	
IF THE ANSWER TO QUESTION 1a IS 0 SKIP TO QUESTION 2. IF IT IS SCORED ≥1 ASK:						
1b. Did you intend to die as a result of this accident?	NO	YES				
Over the past week, how much did you:						
2. think that you would be better off dead or wish you were dead?	0	1	2	3	4	
3. want to harm yourself or to hurt or to injure yourself?	0	1	2	3	4	
4. think about suicide?	0	1	2	3	4	
5. plan for a suicide?	0	1	2	3	4	
6. take active steps to prepare for a suicide attempt in which you expected or intended to die?	0	1	2	3	4	
7. Over the past week did you injure yourself intentionally? IF NO, SKIP TO QUESTION 8: IF YES, ASK:	NO	YES				
Over the past week, how seriously did you:						
7a. intentionally injure yourself without suicidal intent?	0	1	2	3	4	
8. attempt suicide?	0	1	2	3	4	
					total	

25 APPENDIX S: COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Frequency ____
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration ____
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability ____
Could /can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents ____
Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation ____
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others.
(2) Mostly to get attention, revenge or a reaction from others.
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).
(0) Does not apply

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you _____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

26 APPENDIX T: DISCONTINUATION EMERGENT SIGNS AND SYMPTOMS SCALE

Instructions:

Please ask the subject, "During the past 7 days, have you experienced any changes in the following symptoms?"

- A "New Symptom" is any symptom that appeared within the 7 days prior to the administration of the DESS.
- An "Old Symptom" is any symptom that appeared before the 7 days prior to the administration of the DESS, AND which continues into the 7 day period. Old Symptoms may be classified as unchanged, improved, or worse.
- *An "Old Symptom (but worse)" or "New Symptom" will require clinician review. It should be noted that some symptoms may be attributed to depression, a "Worsening of depression," "Discontinuation Syndrome," or a specific cause or concurrent illness.
- The clinician will reconcile symptoms reported on the DESS in the source document and record any syndrome(s) or individual symptoms not attributed to a syndrome on the adverse event case report form.

Symptom	Symptom Not Present	Old Symptom, (but unchanged)	Old Symptom, (but improved)	Old Symptom, (but worse)*	New Symptom*
1. Nervousness or anxiety					
2. Elevated mood, feeling high					
3. Irritability					
4. Sudden worsening of mood					
5. Sudden outbursts of anger ("anger attacks")					
6. Sudden panic or anxiety attacks					
7. Bouts of crying or tearfulness					
8. Agitation					
9. Feeling unreal or detached					
10. Confusion or trouble concentrating					
11. Forgetfulness or problems with memory					
12. Mood swings					
13. Trouble sleeping; insomnia					
14. Increased dreaming or nightmares					
15. Sweating more than usual					
16. Shaking, trembling					

Symptom	Symptom Not Present	Old Symptom, (but unchanged)	Old Symptom, (but improved)	Old Symptom, (but worse)*	New Symptom*
17. Muscle tension or stiffness					
18. Muscle aches or pains					
19. Restless feeling in legs					
20. Muscle cramps, spasms, or twitching					
21. Fatigue, tiredness					
22. Unsteady gait or incoordination					
23. Blurred vision					
24. Sore eyes					
25. Uncontrolled mouth/tongue movements					
26. Problems with speech or speaking clearly					
27. Headache					

27 APPENDIX U: ANALYSIS OF PAROXETINE USERS IN THE AERS DATABASE

Overview

The purpose of this analysis is to determine whether the patterns of adverse event reporting for paroxetine at doses of 10 mg are different than the patterns of reporting for paroxetine at doses >10 mg in women aged 40 to 65 years as reported in the Adverse Event Reporting System (AERS) of the FDA. Particular focus is on major cardiovascular events and events related to suicidality, bone fracture, and abnormal bleeding.

The following analysis report was produced from the 2012 Q2 release of the AERS database, which was made publicly available by the FDA in early October 2012.

Analysis results

The AERS database comprises 3,778,243 cumulative case reports, including 181,428 new reports in the 2012 Q2 quarterly release. Of these case reports, 64,027 referenced use of paroxetine. Where gender was known, 21,199 were males and 40,038 were females. Of the approximately 40,000 females, 12,763 were reportedly between the ages of 40 and 65 years, which is the age and gender group of interest. Where the paroxetine dose was known, the cohort of females aged 40 to 65 years was further segmented into those reporting use of 10 mg (n=512) or >10 mg (n=3392) of paroxetine. All analyses below are carried out on the cohort of paroxetine cases that were reported for women aged 40 to 65 years where dose is also reported (**Table 27-1**).

Table 27-1 Case selection

Selection Rule	N
Case reports in AERS through Q2 2012	3,778,243
AERS cases referencing paroxetine	64,027
Males (paroxetine)	21,199
Females (paroxetine)	40,038
Females (paroxetine, age 40-65)	12,763
Females (paroxetine, aged 40-65 y) 10 mg dose	**512**
Females (paroxetine, aged 40-65 y) >10 mg dose	**3392**

AERS=Adverse Event Reporting System; Q2=second quarter; y=years.

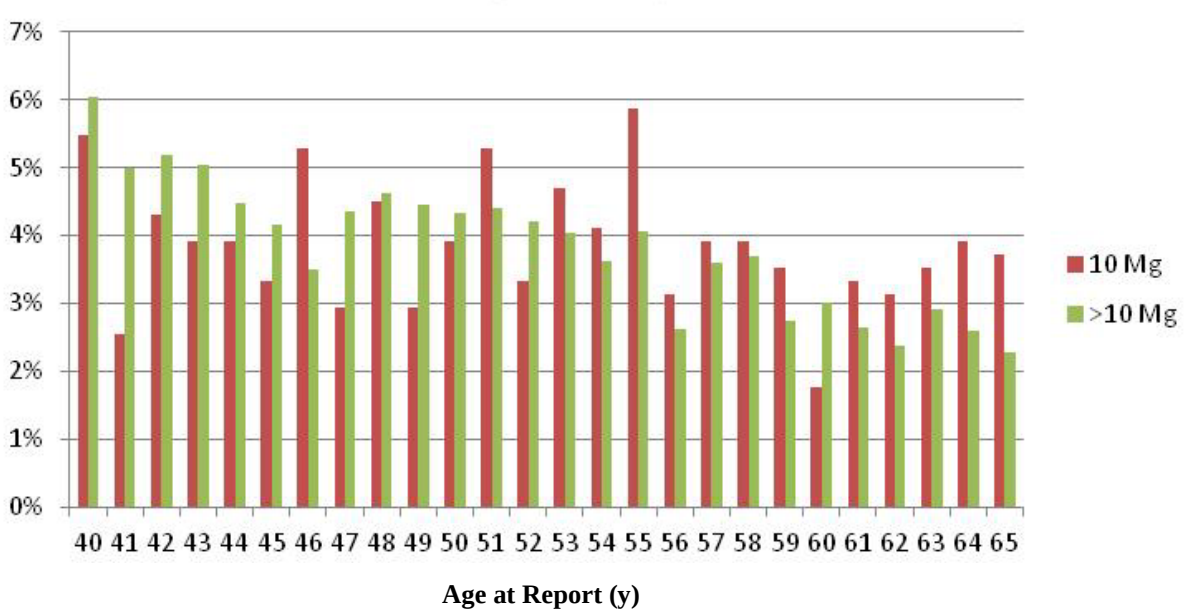
Age analysis

On average, the age listed for the 10 mg cases was slightly older than the >10 mg cases. **Table 27-2** provides the mean and median ages for each group and **Figure 27-1** describes the age distribution.

Table 27-2 Mean and median age

	10 mg	>10 mg
Mean age, years	52.07	50.81
Median age, years	52	50

Figure 27-1 Age distribution



Reported Indications

AERS reports optionally include drug indication. There were 327 indications reported for paroxetine for the 10 mg cases and 2,101 paroxetine indications reported for the >10 mg cases. **Table 27-3** and **Table 27-5** list the top 15 indications reported for the 10 mg and >10 mg cases, respectively. There were 5 reported indications related to menopause, representing 1.53% of indications for paroxetine in the 10 mg group (**Table 27-4**), and 29 indications related to menopause, representing 1.38% of indications reported in the >10 mg group (**Table 27-6**). The

top 15 indications for both dosing groups were generally similar as were the menopause-related indications, indicating that the 10 mg and the >10 mg doses were being prescribed similarly.

Table 27-3 Top 15 indications reported for paroxetine for 10 mg cases

10 mg top 15 reported indications	N	%
Depression	156	47.71
Anxiety	38	11.62
Panic disorder	24	7.34
Drug use for unknown indication	13	3.98
Obsessive-compulsive disorder	10	3.06
Depression NOS	8	2.45
Panic attack	7	2.14
Post-traumatic stress disorder	6	1.83
Insomnia	6	1.83
Product used for unknown indication	5	1.53
Anxiety NEC	4	1.22
Anxiety disorder	4	1.22
Generalized anxiety disorder	3	0.92
Major depression	3	0.92
Depressive symptom	3	0.92

NEC=not elsewhere classified; NOS=not otherwise specified.

Table 27-4 Indications related to menopause for 10 mg cases

10 mg indications related to menopause	N
Hot flushes NOS	1
Flushing	1
Depression postmenopausal	1
Premenstrual syndrome	1
Hot flush	1

NOS=not otherwise specified.

Table 27-5 Top 15 indications reported for paroxetine for >10 mg cases

Greater than 10 mg	N	%
Depression	1132	53.88
Anxiety	187	8.90
Drug use for unknown indication	115	5.47
Panic disorder	111	5.28
Depression NOS	47	2.24
Obsessive-compulsive disorder	41	1.95
Major depression	38	1.81
Panic attack	37	1.76
Product used for unknown indication	37	1.76
Post-traumatic stress disorder	28	1.33
Anxiety NEC	27	1.29
Anxiety disorder	26	1.24
Ill-defined disorder	21	1.00
Generalized anxiety disorder	13	0.62
Social phobia	13	0.62%

NEC=not elsewhere classified; NOS=not otherwise specified.

Table 27-6 Indications related to menopause for >10 mg cases

>10 mg indications related to menopause	N
Premenstrual syndrome	12
Hot flush	8
Menopausal symptoms	3
Premenopause	1
Menopausal disorder	1
Flushing	1
Menopause	1
Hormone replacement therapy	1
Hormone therapy	1

Primary Outcomes

The pattern of reporting primary outcomes among the 10 mg and >10 mg cases was similar, as described in **Figures 27-2** and **27-3,** respectively.

Figure 27-2 Primary outcome for 512 cases using 10 mg

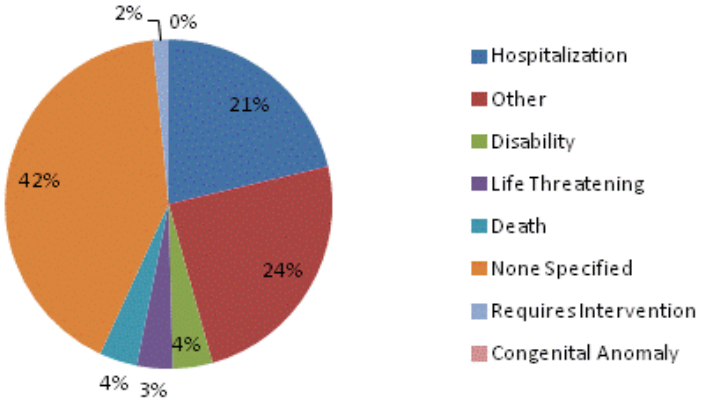
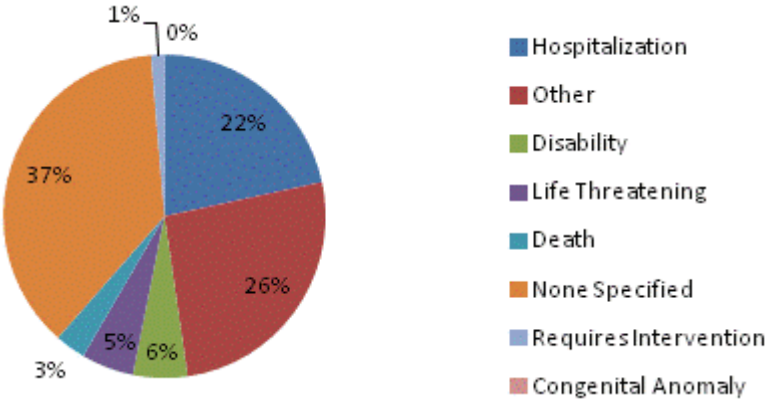


Figure 27-3 Primary outcome for 3392 cases using >10 mg



Data Mining

Data mining signal detection was carried out for the 10 mg and >10 mg cases, focusing on the following event categories:

- Serious cardiac events
- Suicidality
- Abnormal bleeding
- Fractures

In a data mining analysis using a spontaneous reporting database such as AERS, a traditional "denominator" (eg, the number of patients exposed to a particular drug and/or how long they have been exposed) is not known. To overcome this limitation, data mining methods produce a ratio of disproportionate reporting, comparing the number of reports for a particular drug/AE combination to the number of reports for that AE across all of the other drugs in the AERS database or a subset of AERS. For this analysis, all cases for females aged 40 to 65 years were used for the denominator.

A disproportionality ratio of 1 indicates that that the AE is being reported for the drug of interest at the same rate as it is being reported for all other drugs in the background; a ratio of 2 means that it is being reported at twice the background rate. For this analysis, the measure of disproportionality used was the proportional reporting ratio (PRR), which is a common disproportionality measure used throughout the industry. Each PRR result also includes a chi-square measure of confidence.

There is no single international standard for signal detection thresholds based on AERS and other spontaneous report databases. The CIOMS VIII Working Group (CIOMS Geneva 2010) dedicates a chapter (VII) to "more complex quantitative signal detection methods," and provides thoughtful perspectives on the role of statistical analysis in the setting of pharmacovigilance. Despite a lack of standards, signaling is commonly defined by the following threshold for PRR:

- PRR: PRR >2, chi square >4, and number of reports >3

A drug/AE combination that crosses a data mining signal threshold is not necessarily indicative that the drug is the cause of that adverse event. For example, many adverse events that produce high disproportionality scores are related to the reported drug's indication. Therefore, disproportionality results should be interpreted in the context of other information known about the drug.

Tables 27-7 and **27-8** list the highest 15 disproportionality scores for the 10 mg and >10 mg groups, respectively. Although the events of interest were not remarkably different between the two dosing groups, the strengths of the disproportionality signal were far greater in the >10 mg group compared to the 10 mg group. This would reflect a dose effect in that the disproportionality scores were correspondingly higher in the higher dose group.

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Table 27-7 Top 15 scores for 10 mg cases

	10 mg (512 total cases)			AERS Total
Event of Interest	**Cases**	**PRR**	**Chi-Sq**	**Cases**
Drug withdrawal syndrome	61	18.54	987.13	4379
Anxiety	56	4.91	173.54	15032
Insomnia	51	4.15	121.42	16171
Dizziness	66	3.21	102.06	27049
Nausea	85	2.47	78.33	45159
Panic attack	19	10.60	155.10	2370
Tremor	35	4.36	88.27	10578
Hyperhidrosis	31	4.74	88.46	8621
Suicidal ideation	24	6.20	99.83	5103
Paresthesia	34	4.05	76.02	11056
Agitation	22	6.07	88.32	4780
Brugada syndrome	5	211.64	730.27	36
Crying	17	7.92	95.87	2832
Tinnitus	17	7.11	83.21	3154
Nervousness	18	5.08	55.13	4668

AERS=Adverse Event Reporting System; Chi-Sq=chi-square; PRR= proportional reporting ratio.

Table 27-8 Top 15 scores for >10 mg cases

	10 Mg (512 total cases)			AERS Total
Event of Interest	Cases	PRR	Chi-Sq	Cases
Drug withdrawal syndrome	494	25.08	10179.36	4379
Anxiety	354	4.76	1045.58	15032
Suicidal ideation	208	8.38	1300.00	5103
Dizziness	420	3.11	615.09	27049
Crying	137	10.03	1055.48	2832
Depression	304	3.74	610.57	16346
Tremor	220	4.19	528.36	10578
Insomnia	277	3.44	479.83	16171
Agitation	146	6.22	618.73	4780
Nightmare	100	10.07	770.96	2059
Serotonin syndrome	74	15.65	927.80	1007
Paresthesia	208	3.78	421.93	11056
Hyperhidrosis	182	4.25	446.04	8621
Weight increased	228	3.45	395.68	13257
Disturbance in attention	96	6.67	444.28	2934

AERS=Adverse Event Reporting System; Chi-Sq=chi-square; PRR= proportional reporting ratio.

Table 27-9 provides the data mining results for Preferred Terms of interest that appeared in either the 10 mg or >10 mg subgroup. Events of interest that met the signal threshold (PRR >2, chi square >4, and number of reports >3) are highlighted below. There were no signals that met

the significance threshold among the serious cardiac events or the bone fracture-related terms of interest for either dosing group. For suicidality-related events that met the disproportionality threshold, both suicide ideation and suicide attempt were signals in both dosing subgroups, although the disproportionality scores were far higher in the higher dosing group. Three Preferred Terms of interest, self-injurious ideation, intentional self-injury, and suicidal behavior met the signal threshold in the >10 mg dose group only. For Preferred Terms of interest related to abnormal bleeding, bone marrow failure met the signal threshold in the 10 mg subgroup only. The preferred term thrombocytopenic purpura met the signal threshold in the >10 mg subgroup.

Table 27-9 Data mining results for 10 mg and >10 mg cases

	10 Mg (512 total cases)			>10 Mg (3392 Total Cases)			AERS Total Female 40-65
Terms of Interest	Cases	PRR	Chi-Sq	Cases	PRR	Chi-Sq	Cases
Serious cardiac events							
Cardio-respiratory arrest	3	1.59	0.20	7	0.56	2.01	2475
Cardiac arrest	1	0.27	1.31	10	0.41	8.07	4851
Myocardial infarction	1	0.11	6.16	13	0.22	35.17	11552
Cardiac failure	0	0.00	0.00	9	0.71	0.80	2514
Atrioventricular block complete	0	0.00	0.00	6	3.39	7.73	355
Supraventricular tachycardia	0	0.00	0.00	6	1.48	0.52	804
Torsade de pointes	0	0.00	0.00	6	1.79	1.35	669
Acute coronary syndrome	0	0.00	0.00	2	1.12	0.05	355
Cardiogenic shock	0	0.00	0.00	2	0.78	0.00	509
Cardiac failure acute	0	0.00	0.00	1	1.38	0.07	144
Cardiopulmonary failure	0	0.00	0.00	1	1.27	0.11	156
Atrioventricular block 1st degree	0	0.00	0.00	1	0.69	0.00	288
Atrioventricular block 2nd degree	0	0.00	0.00	3	3.54	3.16	170
Cardiac failure congestive	0	0.00	0.00	23	0.86	0.41	5313
Coronary artery occlusion	0	0.00	0.00	5	0.86	0.02	1156
Congestive cardiomyopathy	0	0.00	0.00	4	2.36	1.88	339
Suicidality							
Suicidal ideation	24	6.20	99.83	208	8.38	1300.00	5103
Suicide attempt	8	3.29	10.59	87	5.52	310.05	3198
Completed suicide	5	1.49	0.39	23	1.03	0.00	4417
Self-injurious ideation	1	6.66	0.81	6	6.16	20.40	198
Intentional self-injury	1	4.90	0.43	15	11.65	128.02	269
Suicidal behavior	0	0.00	0.00	6	6.54	22.13	187
Depression suicidal	0	0.00	0.00	2	3.21	1.21	125
Self-injurious behavior	0	0.00	0.00	1	0.87	0.11	228
Abnormal Bleeding							
Thrombocytopenia	5	1.22	0.04	16	0.59	4.20	5372

Bone marrow failure	4	4.01	6.26	4	0.60	0.69	1314
Pancytopenia	3	1.44	0.08	2	0.14	9.36	2741
Hypoprothrombinemia	1	57.05	12.71	0	0.00	0.00	128
Bone marrow toxicity	1	23.02	4.71	1	3.46	0.15	58
Bone marrow disorder	1	10.58	1.72	0	0.00	0.00	125
Idiopathic thrombocytopenic purpura	0	0.00	0.00	7	3.55	10.21	396
Disseminated intravascular coagulation	0	0.00	0.00	4	0.64	0.50	1243
Hemorrhagic anemia	0	0.00	0.00	2	3.29	1.28	122
Coagulopathy	0	0.00	0.00	2	0.42	1.10	949
Hemorrhagic diathesis	0	0.00	0.00	1	1.26	0.11	157
Hemorrhagic disorder	0	0.00	0.00	1	4.38	0.31	46
Bone Fractures							
Pathological fracture	0	0.00	0.00	4	1.92	0.96	414
Fracture malunion	0	0.00	0.00	1	9.39	1.37	22

AERS=Adverse Event Reporting System; Chi-Sq=chi-square; PRR= proportional reporting ratio.

Discussion

Cases reported into the AERS database for female paroxetine users aged 40 to 65 years were similar between the two dosing groups of 10 mg and >10 mg with respect to age, top 15 indications for use, menopause-related indications for use, and primary outcome. When signals of disproportionality were examined, the events of interest for the top 15 scores that met the signal threshold were not remarkably different between the 2 dosing groups, but the higher dosing group had disproportionality scores that were much higher than those reported for the lower dosing group.

When examining Preferred Terms of interest relating to major cardiovascular events, suicidality, abnormal bleeding, and bone fracture, differences were found between the 10 mg and >10 mg dosing groups with respect to the number and strength of terms of interest that met the signal threshold for suicidality with the number and strength of the signals being higher in the >10 mg dose group. No conclusions could be drawn from the abnormal bleeding terms of interest as different signals met the threshold in the different dosing groups.

From this analysis, certain events of interest and signal scores appear to be greater in the cases of female paroxetine users aged 40 to 65 years reported into AERS in the >10 mg compared with the 10 mg dose group.

28 APPENDIX V: REFERENCES

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